

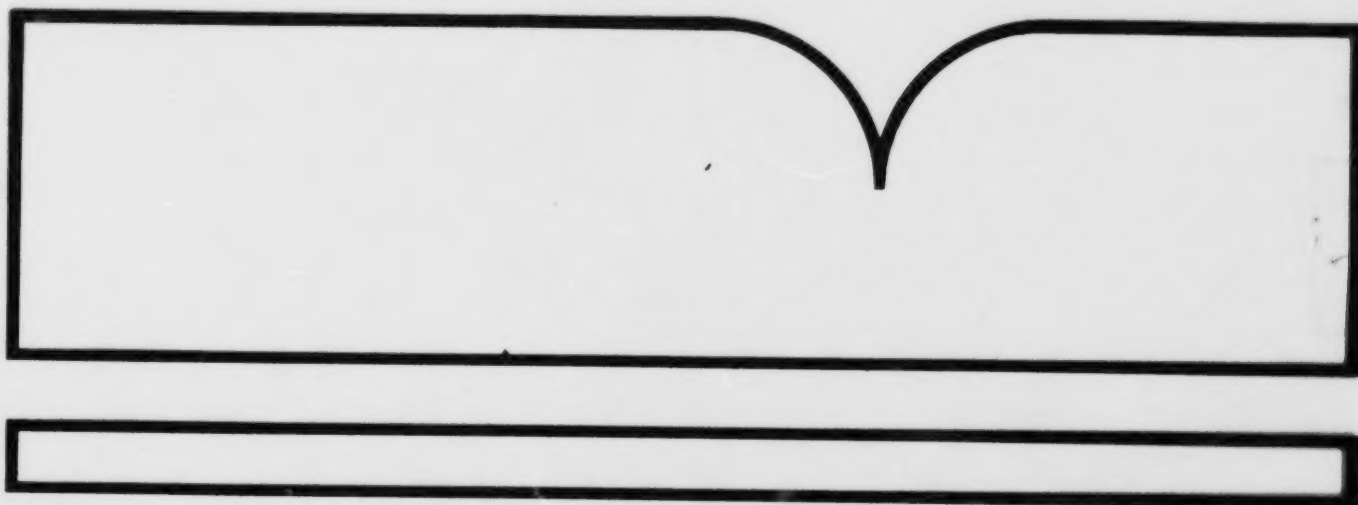
Investigation of Selected
Potential Environmental
Contaminants: Haloalcohols

Syracuse Research Corp., NY

Prepared for

Environmental Protection Agency
Washington, DC

Mar 80



U.S. Department of Commerce
National Technical Information Service

NTIS

INVESTIGATION OF SELECTED
POTENTIAL ENVIRONMENTAL CONTAMINANTS:
HALOALCOHOLS



March 1980

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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16. ABSTRACT This report reviews the potential environmental hazard associated with the commercial use of a large group of chemicals that are used mostly as chemical intermediates - haloalcohols. Ten commercial compounds are covered in the report including the following large commercial products: 2-chloroethanol (ethylene chlorohydrin) -intermediate for ethylene oxide; 2-chloro-1-propanol and 1-chloro-2-propanol (propylene chlorohydrin) -intermediate for propylene oxide; 2,3-dichloro-1-propanol and 1,3-dichloro-2-propanol (α - and β -dichlorohydrin) -intermediate for epichlorohydrin. Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination, as well as information related to health and biological effects, are reviewed.		
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ENVIRONMENTAL CONTAMINANTS:

HALOALCOHOLS

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March 1980
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EXECUTIVE SUMMARY

Ten haloalcohols have been reviewed in this report. Three of these (2,2,2-trichloroethanol, 2,2,2-trifluoroethanol, and 2-bromopropanol) are produced as specialty or laboratory chemicals, the annual production of each being estimated at less than 0.1 million pounds. 2,3-Dibromo-1-propanol is primarily consumed as a fire retardant; its annual production was placed at <10 million pounds. 2-Chloroethanol production was estimated at 50 to 100 million pounds per year. Its occasional use as an intermediate for ethylene oxide synthesis accounts for the higher estimated production. 2-Chloroethanol is also consumed as an intermediate in a variety of syntheses. The remaining chloropropanols, which are primarily consumed as non-isolated intermediates, have annual production and major use as follows: monochloropropanols (1-chloro-2-propanol and 2-chloro-1-propanol) - 1950 million pounds, for propylene oxide production; dichloropropanols (1,3-dichloro-2-propanol and 2,3-dichloro-1-propanol) - 585 million pounds, for epichlorohydrin production; and 3-chloro-1,2-propanediol - 195 million pounds, for glycerin production.

The occurrence and distribution of haloalcohols in the environment has been only partially described. For the most part, these chemicals are used as chemical intermediates. No information was available on atmospheric emissions released during production. Haloalcohols have been identified in waste waters and in liquid wastes (such as still pot residues). The exact way that these wastes are treated is unknown. Inadvertent formation of chloroethanol, bromoethanol, and chloropropanol results when the corresponding epoxide (ethylene oxide or propylene oxide) reacts with halide ion. The precursor epoxides are fumigants and sterilants for a variety of commodities, medical devices, drugs and other materials coming into close contact with people.

Although total estimated epoxide application for these purposes is less than 0.1 million pounds, the close contact with humans makes this mode of exposure potentially hazardous.

Chemodynamic properties indicate that with the possible exception of trifluoroethanol, the haloalcohols considered in this report are not persistent and are degraded in the environment to the corresponding glycols. Based upon their solubility in water, it appears likely that they will be transported with flowing water. Other means of transport cannot be conclusively predicted from the available information.

The haloalcohols have demonstrated fatal toxicity in man following acute oral, dermal, or inhalation exposure. Target organs include the central nervous system, liver, kidneys, and lungs. Fatal toxicity is often seen after a delay of several hours or days following exposure. Fluoroethanol and chloroethanol are the most toxic agents of this group, demonstrating lethal toxicity at levels of 2 to 100 mg/kg in different animal species; trifluoroethanol and trichloroethanol exhibit toxicity at levels three to tenfold higher. Absorption through the skin is rapid, and dermal contact does not produce marked immediate irritation. Inhalation may result in cumulative effects, particularly in the liver and kidneys. The haloalcohols are irritating to the eyes, and direct contact with high concentrations may produce irreversible corneal changes. Liver damage produced by the haloalcohols potentiates the toxic effects of drugs and chemicals that would be normally metabolized at this site.

Adverse reproductive effects have been seen with 2,2,2-trifluoroethanol and 3-chloro-1,2-propanediol. The latter has been studied extensively as a posttesticular antifertility agent. Both low-dose reversible effects on sperm function and high-dose irreversible effects have been observed following administration to animals for one or two weeks.

Animal studies have indicated that 2-chloroethanol and 3-chloro-1,2-propanediol may adversely affect bone marrow cells. The relevance of these effects, involving cell shape and chromosome aberrations, is not clear since they appear to be reversible after exposure is terminated.

Several of the haloalcohols have been shown to be mutagenic in microbial systems. In addition, 2-chloroethanol produced teratogenic effects in the chick embryo. A single study in rats has indicated that 2-chloroethanol may cause an increase in pituitary tumors. These studies indicating mutagenic and possible carcinogenic effects in animals have not been confirmed in the human population since epidemiological investigations and controlled human studies with the haloalcohols have not been reported.

The studies of haloalcohol effects in experimental bioassay systems indicate that these agents do have biologically significant interactions. Extrapolation of these data to man and determination of the quantities of these compounds that will produce effects in the human population cannot be implemented with the currently available information.

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I. Physical and Chemical Data

A. Structure and Properties

1. Chemical Structure and Nomenclature

The ten haloalcohols reviewed herein are derivatives of ethanol, 1- or 2-propanol or 1,2-propanediol which contain one or more halide atoms (fluoride, chloride, or bromide). Table 1 lists the following information on the haloalcohols under study: International Union of Pure and Applied Chemistry (IUPAC) system names, common names, molecular formulae, molecular structures, and CAS numbers. These ten compounds were selected because of their commercial significance; however in some cases, information on environmental fate and toxicity on other haloalcohols will be reviewed when the information is available.

Throughout this review the haloalcohols are referred to by their IUPAC system names. In this system, the names are based upon the parent alcohol and the carbon skeleton is numbered from the end of the chain closest to the alcohol group (OH). The skeletons and numbering for the parent alcohols of the haloalcohols under review are as follows:

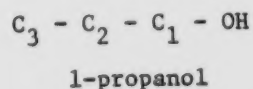
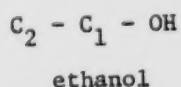
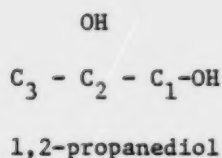
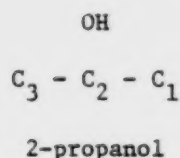


Table 1. Structure and Nomenclature of Haloalcohols

Molecular Formula	Molecular Structure	CAS Registry Number	IUPAC System Name	Synonymous Trivial Names
C_2H_5BrO	$BrCH_2CH_2OH$	540-51-2	2-Bromoethanol	β -Bromoethyl alcohol Ethylene bromohydrin Glycol bromohydrin 2-Bromo-1-hydroxyethane
C_2H_5ClO	$ClCH_2CH_2OH$	107-07-3	2-Chloroethanol	β -Chloroethyl alcohol Ethylene chlorohydrin Glycol chlorohydrin Chloro-1-hydroxyethane
$C_2H_3Cl_3O$	Cl_3CCH_2OH	115-20-8	2,2,2-Trichloroethanol	Trichloroethyl alcohol 2,2,2-Trichloro-1-hydroxyethane
$C_2H_3F_3O$	F_3CCH_2OH	78-89-8	2,2,2-Trifluoroethanol	Trifluoroethyl alcohol 2,2,2-Trifluoro-1-hydroxyethane
C_3H_7ClO	$CH_3CHClCH_2OH$	78-89-7	2-Chloro-1-propanol	β -Chloropropyl alcohol Propylene- β -chlorohydrin 2-Chloro-1-hydroxypropane
C_3H_7ClO	$CH_3CHOHCH_2Cl$	127-00-4	1-Chloro-2-propanol	β -Chloroisopropyl alcohol Propylene α -chlorohydrin sec-Propylene chlorohydrin 1-Chloro-2-hydroxypropane
$C_3H_6Br_2O$	$BrCH_2CHBrCH_2OH$	96-13-9	2,3-Dibromo-1-propanol	β -Dibromohydrin Glycerin - α , β -dibromohydrin 2,3-Dibromo-1-hydroxypropane

Table 1. (Continued)

<u>Molecular Formula</u>	<u>Molecular Structure</u>	<u>CAS Registry Number</u>	<u>IUPAC System Name</u>	<u>Synonymous Trivial Names</u>
$C_3H_6Cl_2O$	$ClCH_2CHClCH_2OH$	616-23-9	2,3-Dichloro-1-propanol	β, γ -Dichloropropyl alcohol Allyl alcohol dichloride Assym. glycerin dichlorohydrin β -Dichlorohydrin 2,3-Dichloro-1-hydroxy propane
$C_3H_6Cl_2O$	$ClCH_2CHOHCH_2Cl$	96-23-9	1,3-Dichloro-2-propanol	β, β' -Dichloroisopropyl alcohol Glycerin α, α' -dichlorohydrin α -Dichlorohydrin 1,3-Dichloro-2-hydroxypropane
$C_3H_7ClO_2$	$HOCH_2CHOHCH_2Cl$	96-24-2	3-Chloro-1,2-propanediol	α -Monochlorohydrin α -Chlorohydrin 3-Chloro-1,2-dihydroxy propane



Several alternative, common nomenclature systems exist for haloalcohols. The most widely used common system names the haloalcohols as "olefin halohydrins"; 2-chloroethanol is called ethylene chlorohydrin and the monochlorinated propanols are referred to as propylene chlorohydrin. The literature very often refers to the haloalcohols by this system rather than by the IUPAC nomenclature.

2. Physical Properties of the Pure Material

The haloalcohols are characterized as colorless, dense, hygroscopic liquids at ambient temperature (Lichtenwalter and Riesser, 1964). Their odors are characterized as "ether-like" or "ethanol-like" (Windholz, 1976; Halocarbon Products, 1967). The hydroxide group and its ability to hydrogen bond have dominant influence upon physical properties. The halide substituents affect the physical properties through its addition to molecular weight and its inductive and electronic effects. Table 2 lists the salient physical properties of the ten haloalcohols. The brominated and chlorinated ethanol and propanol derivatives have similar properties, while trifluoroethanol and chloropropanediol differ considerably.

Table 2. Physical Properties of Haloalcohols (Adapted from Beilsteins Handbuch der Organischen Chemie - Prager and Jacobson, 1918; Richter, 1928, 1941, 1958; Lange, 1967; McCabe and Warner, 1948; Hodgeman, 1961; Windholz, 1976; and manufacturers data - Aldrich Chemical Co., 1977; Halocarbon Products, 1967; Great Lakes, 1972 - Ballinger and Long, 1959; 1960)

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Property	BrCH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OH
Molecular Weight (g)	126.97	158.42	186.27	214.12	242.07	270.02	297.97	325.92	353.87
Melting Point (°C)	-80.26	-73.6	-65.10	-55.10	-45.10	-35.10	-25.10	-15.10	-5.10
Boiling Point (°C)	156-158 (750 torr)	127.9-128.1 (760 torr)	131 (737 torr)	134 (730 torr)	137 (720 torr)	140 (710 torr)	143 (700 torr)	146 (690 torr)	149 (680 torr)
ΔH Vaporization	12.97 cal/mole at 126.97°	12.97 cal/mole at 127.9°	12.97 cal/mole at 131°	12.97 cal/mole at 134°	12.97 cal/mole at 137°	12.97 cal/mole at 140°	12.97 cal/mole at 143°	12.97 cal/mole at 146°	12.97 cal/mole at 149°
Density 20/4 (g/cc)	1.7720	1.20190	1.18118	1.16022	1.13926	1.11830	1.09734	1.07638	1.05542
n _D ²⁰	1.49648	1.4421	1.4221	1.4022	1.3823	1.3624	1.3425	1.3226	1.3027
Vapor pressure (torr)	-	6.27 (17.5°C)	-	-	-	-	-	-	-
Disassociation Constant K _a (water)	2.7 × 10 ⁻¹⁷ (25°C)	1.6 × 10 ⁻¹⁷ (25°C)	3.6 × 10 ⁻¹⁷ (25°C)	5.6 × 10 ⁻¹⁷ (25°C)	-	-	-	-	-
Solubility	Misc. water soluble most org. solvents except per ethal	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other	Misc. water alcohol, other
Acetone with water (°C)	99.1° (762.4 torr)	97.45°	95.4°	93.4°	91.4°	89.4°	87.4°	85.4°	83.4°
Viscosity (cP, 20°C)	0.01995 g/cm sec (20°)	0.02486 g/cm sec (20°)	0.02977 g/cm sec (20°)	0.03468 g/cm sec (20°)	0.03959 g/cm sec (20°)	0.04450 g/cm sec (20°)	0.04941 g/cm sec (20°)	0.05432 g/cm sec (20°)	0.05923 g/cm sec (20°)
ΔH combustion (cal/mole, 20°C)	-	1044 cal/g	1044 cal/g	1044 cal/g	1044 cal/g	1044 cal/g	1044 cal/g	1044 cal/g	1044 cal/g
Flash Point, °F	-	115	115	115	115	115	115	115	115

Although the pure materials are colorless liquids, the brominated and chlorinated alcohols usually appear slightly colored since they partially decompose and turn yellow as they age. Trifluoroethanol appears to be an exception since it is more stable (see Subsection I.B.1). Since the haloalcohols have flash points in excess of 100°F, they are not classified as flammable liquids by DOT standards. Also, dibromopropanol is a fire-retardant and does not support combustion (Great Lakes Chemical, 1972).

The haloalcohols as a class are water soluble. Bromoethanol, chloroethanol, trifluoroethanol, and chloropropanediol are miscible in all proportions with water. The least soluble are trichloroethanol and the dihalopropanols. When available, water solubility data for the individual haloalcohols are included in Table 2.

Vapor pressure data was only available for four haloalcohols. Trifluoroethanol, unlike the chlorinated and brominated alcohols, is fairly volatile. It has a vapor pressure of 53 torr at ambient temperature (20°C). Chloropropanediol, at the other extreme, has a vapor pressure of 0.02 torr (20°C). This low vapor pressure is attributed to greater hydrogen bonding by glycols. The vapor pressure data for chloroethanol (6.3 torr, 17.5°C) is the only other value available for ambient temperature. By comparing the molecular formula and boiling point, it is reasonable to estimate about 5 to 10 torr (ambient temperature) for vapor pressure of the monochloropropanols and lower vapor pressures of the remaining haloalcohols.

The haloalcohols will dissociate in water according to the equilibrium:

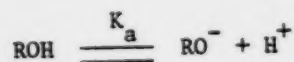
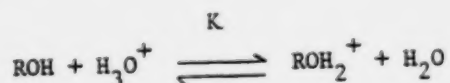


Table 2 lists the ionization constants, K_a , for four haloalcohols. Two of these, bromoethanol and chloroethanol, are weaker acids than water by approximately three orders of magnitude. Trifluoroethanol and trichloroethanol are slightly more acidic than water (Roberts et al., 1956).

Levitt and Levitt (1971) have determined the basicity constants of alcohols in aqueous solution:



They reported pK of -4.20 to -4.30 and -4.27 to -4.35 for trichloroethanol and trifluoroethanol, respectively.

Trifluoroethanol is a useful solvent because of the combined properties of its ionization constant (Halocarbons Products, 1967), high ionizing power, and low nucleophilicity (Harris et al., 1974; Schadt et al., 1974). It is an excellent solvent for organic reactions which require the formation of a carbonium ion.

Haloalcohols do not absorb U.V. light above the cut-off for natural sunlight, 300 nm (Calvert and Pitts, 1966). From the limited information available, the compounds do appear to absorb at lower wavelengths. Continuous absorption is reported below 214 nm for liquid bromoethanol and below 221 nm and 204 nm for chloroethanol as liquid and vapor, respectively (Richter, 1958).

3. Physical Properties of Commercial Materials

Because the bulk of chloroalcohols produced are captive intermediates, relatively small amounts are refined for sales (see Subsection II.B.1). The commercial materials are marketed in high purity and do not significantly differ in properties from the pure materials.

In some applications, freedom from certain impurities is more important than chemical uniformity. Chloropropanols, for example, are produced and sold as isomeric mixtures for certain purposes. While the mixtures naturally differ physically in minor ways from the pure isomers, the differences are of no consequence in their chemical intermediate application.

Table 3 summarizes specifications for the commercial haloalcohols.

4. Principle Contaminants of Commercial Products

Because preparation methods vary for the different haloalcohols, the impurities also differ. Relatively little information on impurities was available and none was quantitative.

The mono- and dichloroalcohols are produced by similar reaction sequences and as the result of analogous side reactions, similar impurities are formed. As discussed above (see Subsection I.A.3) relatively little information was available which described specifications or impurities of the small amounts of these haloalcohols refined for commercial markets. So the information on these impurities is not always verified.

Chloroethanol, chloropropanols, and dichloropropanols are prepared by the addition of hypochlorous acid (HOCl) to ethylene, propylene and allyl chloride, respectively (see Section II.A.3). Major by-products of this reaction are chlorinated ethers and chlorinated olefins. Subsequent cyclization reactions could yield the corresponding epoxides. Propylene chlorination to produce allyl chloride can produce dihalopropenes as well. In summary, potential impurities in each compound are as follows:

Table 3. Commercial Specifications for Haloalcohols
(Adapted from Manufacturers' Product
Data Sheets)

	<u>2,3-Dibromo-1-propanol</u>	<u>2-Chloroethanol</u> ³	<u>2,2,2-Trichloroethanol</u> ⁴
Appearance	clear liquid, no suspended matter	clear liquid, pale amber	colorless liquid
Color, APHA max	50 ¹		
Water, %, max	0.05 ¹ , 0.1 ²		
Acidity, mgKOH/gm max	0.05 ¹ , 0.1 ²		
Bromine, %	73 ²		
Viscosity, _____	33 ²		
Assay		98% min	98% min

¹ Great Lakes Chemical Co., West Lafayette, Indiana

² Velsicol, Chicago, Illinois

³ Evans Chemetics, Darian, Connecticut

⁴ Aldrich Chemical Co., Milwaukee, Wisconsin

In dichloropropanols (Gruber, 1976)

cis- and trans- 1,3-Dichloropropene
1,2-Dichloropropene
1,2,3-Trichloropropene
Chlorinated ethers
Chlorinated saturated and unsaturated,
short-chained aliphatic hydrocarbons
Epichlorohydrin

In chloroethanol (Lichtenwalter and Riesser, 1964)

Ethylene dichloride
Vinyl chloride
Chlorinated ethers
Ethylene oxide
Ethylene glycol

In chloropropanols

Chloropropylenes
Chlorinated ethers
Epichlorohydrin
Propylene glycol

3-Chloro-1,2-propanediol is an intermediate during dichloropropanol conversion to glycerin (see Subsection II.A.3). The by-products already present in the dichloropropanols are potential impurities of 3-chloro-1,2-propanediol. Glycidol which is an intermediate in the reaction sequence and glycidol ethers which are formed as by-products are potential impurities.

Bromoethanol production, which consists of the addition of hydrogen bromide to ethylene oxide, could be accompanied by brominated ether formation as a by-product (see Subsection II.A.3) and therefore brominated ethers are potential contaminants.

Trifluoroethanol is manufactured by the reduction of trifluoroacetyl chloride (see Subsection II.A.3). An intermediate of this reduction is trifluoroacetaldehyde, and, therefore, it is a possible contaminant. Trichloroethanol, which is similarly prepared, has trichloroacetaldehyde as a potential contaminant.

2,3-Dibromo-1-propanol is manufactured by catalyzed bromine addition to allyl alcohol (see Subsection II.A.3). The major side reaction yields 1,2,3-tribromopropane (Clemons and Overbeek, 1966). Other by-products are brominated ethers, brominated short-chain hydrocarbons and isomeric brominated propyl alcohols. Also, epoxide (epibromohydrin) forms during storage and handling (Great Lakes, 1972).

B. Chemistry and Environmental Chemical Reactions

The environmental chemistry of the selected haloalcohols has been estimated from laboratory studies on their hydrolysis, oxidation, and free-radical reactions. Haloalcohols are expected to react in water and in the atmosphere.

Water chemistry of the haloalcohols included hydrolysis reactions (which would be present in any aqueous solution) and oxidation reactions (which may assume importance in water purification processes). Haloalcohols, with the possible exception of trifluoroethanol, will be hydrolyzed in aqueous solution by a complex kinetic scheme to yield glycols. In alkaline solution the process initiates with cyclization to epoxides. At neutral or acid pH, hydrolysis yields glycol directly. The description of haloalcohol oxidation was derived from studies of reaction with a wide variety of oxidants including permanganate, bromate, bromine, and chlorine. The expected initial products are analogous carbonyl compounds (e.g., halogenated aldehydes and ketones). Under normal conditions of water treatment and potable water distribution, the hydrolysis reactions account for virtually all haloalcohol degradation.

Haloalcohol chemistry in the atmosphere approximately consists of oxidation reactions initiated by atmospheric free-radicals and chemical oxidants.

It would appear that direct photolysis of the haloalcohols does not significantly contribute to degradation since these materials do not absorb ultraviolet light of wavelengths found in sunlight.

1. Hydrolysis and Related Reactions

The hydrolysis reactions of simple haloalcohols have been partially characterized. Most of the work has consisted of mechanistic studies and mainly has evaluated ethylene halohydrins (2-haloethanols). Since most studies evaluated alkaline hydrolysis, the reactions of haloalcohols are best characterized in aqueous alkali. Less information is available concerning their hydrolysis in neutral or acidic solution. Table 4 summarizes the specific rate constant for hydrolysis of various halohydrins. The hydrolysis kinetics were measured by determining the rate of chloride formation:



The hydrolysis of the chlorohydrins was reviewed by Frost and Pearson (1951). Their characterization remains the most complete description of known data and of predicted behavior. Their review took information from studies by Brønsted et al. (1929), Nilsson and Smith (1933), Winstein and Lucas (1939), McCabe and Warner (1948), Cowan et al. (1950), and Winstein and Grunwald (1948). Virtually all studies since the publication of the Frost and Pearson review support their characterization (Myszkowski et al., 1965).

Table 4. Kinetic Data for Epoxide Formation
from Haloalcohols in Water

Halohydrin (R_1R_2CHOH)		Temperature (°C)	K_{eq}	k_{OH^-} ($l\text{mole}^{-1}\text{min}^{-1}$)	k_{neutral} (min^{-1})
R_1	R_2				
BrCH ₂	H	0		0.987 ^b	
		5		2.03 ^b	
		10		3.95 ^b	
		25	$2.7 \times 10^{-17}{}^b$		
		40			$4.74 \times 10^{-6}{}^c$
		70			$2.07 \times 10^{-4}{}^c$
ClCH ₂	H	18		0.31(est.) ^a	
		0		0.0167 ^b	
		15		0.153 ^b	
		25	$3.6 \times 10^{-17}{}^b$	0.600 ^b	
		30			$5.4 \times 10^{-3}(\text{ext.}){}^d$
		35		2.17 ^b	$8.4 \times 10^{-3}(\text{ext.}){}^d$
		65			$81.6 \times 10^{-7}(\text{ext.}){}^c$
		99			$300 \times 10^{-6}(\text{ext.}){}^c$
FCH ₂	H	30		0.150 ^b	
		40		0.00508 ^b	
		60		0.0380 ^b	
		70			$1.8 \times 10^{-7}{}^c$
CH ₃ CHCl	H	18		1.7(est.) ^a	
		25			$7.8 \times 10^{-3}(\text{est.}){}^d$
CH ₂ Cl	CH ₃	18		6.5 ^a	
		25			$6.0 \times 10^{-3}(\text{est.}){}^d$
(CH ₃) ₂ CCl	H	18		77 ^a	$0.393 \times 10^{-2}{}^a$
(CH ₃) ₂ CCl	CH ₃	18		633 ^a	$0.206 \times 10^{-2}{}^a$
(C ₂ H ₅) ₂ CCl	H	18		358 ^a	$2.67 \times 10^{-2}{}^a$

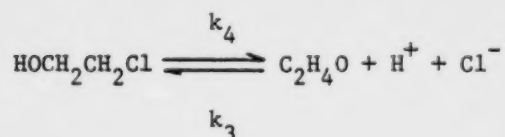
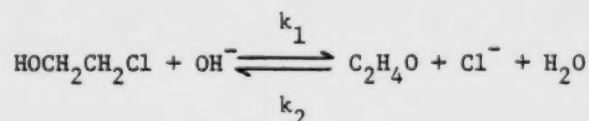
(a) Nilsson and Smith, 1933

(b) McCabe and Warner, 1948

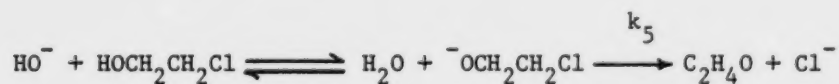
(c) Cowan et al., 1950

(d) Ketola et al., 1978

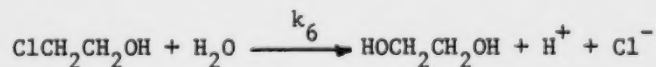
Frost and Pearson considered pathways by which the chlorohydrins hydrolyze to initially yield epoxides or glycols. The epoxide, when it is formed, is in equilibrium with the halohydrin. They demonstrated the equilibria with 2-chloroethanol:



The specific rate constants k_1 , k_2 , and k_3 were measured and they estimated a value for k_4 from the data as $6.4 \times 10^{-13} \text{ s}^{-1}$ at 20°C . Direct studies on the halohydrin's epoxidation in alkali has demonstrated that the epoxide does form through the anion of the halohydrin:



Direct studies on the hydrolysis of 2-chloroethanol disclosed that it directly hydrolyzed to glycol (Cowan et al, 1950):



The specific hydrolysis rate (estimated to 20°C) was $6 \times 10^{-10} \text{ s}^{-1}$, which is three factors of ten faster than the estimated k_4 .

Some controversy exists over the possible "spontaneous epoxidation" of chlorohydrin. Frost and Pearson suggested that the direct epoxidation could occur when chlorides were activated (for example, tertiary chlorides). None of the selected haloalcohols are expected to epoxidize by this pathway. Ketola and coworkers (1978) recently suggested a so-called "neutral" hydrolysis accompanied the alkali promoted dehydrochlorination of 2-chloroethanol, 1-chloro-2-propanol and 2-chloro-1-propanol. Rates were measured as formation of chloride ion as described above. They estimated the "neutral" reaction (k_o) which accompanied the alkaline reaction (k_{OH}). Observed hydrolysis rate, k_t^- , was expressed as

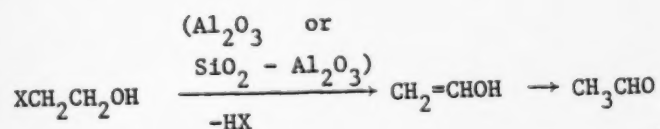
$$k_t^- = k_o + k_{OH} \bar{C}_t$$

where $\bar{C}_t$ was the average hydroxide ion concentrations. The meaning of k_o is not clear. Their estimated values are far faster than measured hydrolysis rates of these or analogous chlorohydrins in neutral aqueous solution. And, they did not define the "neutral" reaction in terms of organic reaction product, i.e., they did not determine if the product was an epoxide.

The haloalcohols can also hydrolyze in alkali by an alternative route of dehydrohalogenation (elimination of HX). This route initially yields carbonyl compound, aldehyde or ketone. This alternative pathway appears controlled by the cation present. Myszkowski and coworkers (1966) reported product distribution for hydrolysis of propylene chlorohydrin mixtures (1-chloro-2-propanol and 2-chloro-1-propanol) with ten cations. They noted a variation in the percentage of acetone; highest production occurred with Ba^{2+} , Ca^{2+} and Co^{2+} , and lowest production with K^+ . Zimakov and Kogan (1951) have

described the product composition from refluxing aqueous suspensions of magnesium hydroxide or nickel hydroxide with mixtures of 1-chloro-2-propanol and 2-chloro-1-propanol (ratios of 91:9 and 75:25). Table 5 summarizes their results. The authors concluded that propionaldehyde directly forms from 2-chloro-1-propanol and is not a subsequent rearrangement product derived from propylene oxide. The authors did not speculate on the reason allyl alcohol was a major product from reflux with nickel hydroxide but a minor product from reflux with magnesium hydroxide. Also, it is noteworthy that Zimakov and Kogan did not report any acetone production.

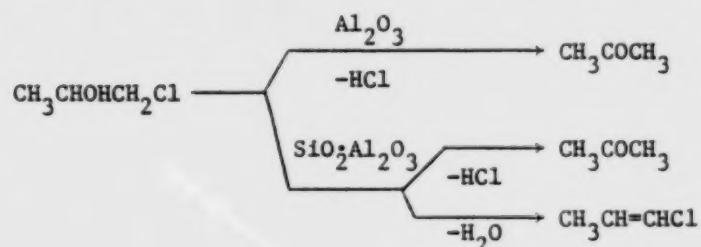
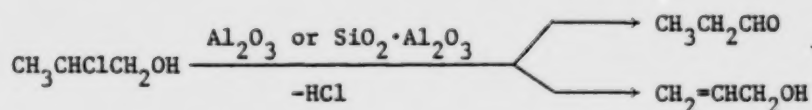
Chloroethanol, bromoethanol, and the chloropropanols react over solid acid or solid base (aluminosilicates, metal oxides, molecular sieves, etc.) to yield a variety of products (Anju et al., 1973; Mochida et al., 1972). Reactions observed included dehydrohalogenation, dehydration, and elimination of HOCl. On solid acid, (e.g., the aluminosilicates) the reactions appeared to pass through carbonium ion intermediates and products were either carbonyl compounds or enols from dehydrohalogenation or aliphatic halides from dehydration:



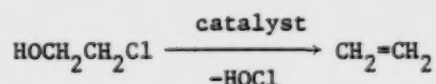
(X=Cl or Br)

Table 5. Dehydrochlorination of Mixtures of Propylene Chlorohydrin (PCH) Isomers in a Boiling Aqueous Suspension of $\text{Mg}(\text{OH})_2$ and $\text{Ni}(\text{OH})_2$ (from Zimakov and Kogan, 1951)

Base	% Base	Isomeric comp of PCH, %	Yield, % of initial PCH					PO + PG PA + AA
		 	undecom- posed PCH	propylene oxide (PO)	propylene glycol (by diff.) (PG)	allyl alcohol (AA)	propional- dehyde (PA)	
Mg(OH) ₂	15	91	9	62.5	22.2	1.9	5.9	11.2
Mg(OH) ₂	15	91	9	52.0	33.4	1.9	5.6	11.4
Mg(OH) ₂	15	91	9	61.6	24.6	1.7	5.6	11.8
Mg(OH) ₂	30	75	25	64.5	23.0	2.3	6.4	9.7
Mg(OH) ₂	30	75	25	67.2	6.3	0.2	25.0	2.9
Ni(OH) ₂	20	75	25	69.2	4.2	21.3	0.1	
Ni(OH) ₂	20	75	25	69.8	3.6	21.6	0.1	
Ni(OH) ₂	20	75	25	71.8	4.6	5.0	18.3	0.5



On solid bases the halohydrins can yield epoxides. Some transition metals (such as Pt or Pd) can catalyze the HOX elimination and the product is the olefin:

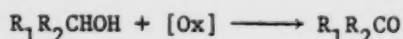


2. Oxidation

The two types of oxidation reactions that have been studied will be discussed separately: (1) chemical oxidants (such as bromine, bromate, permanganate and chloramine-T) and (2) free-radical oxidants. Studies on the chemical oxidants describe the behavior expected when haloalcohols are treated by conditions analogous to those of water disinfection (e.g., chlorination). The latter process, free-radical oxidation, relates to the atmospheric reactions expected to participate in haloalcohol degradation in the photochemical smog cycle.

a. Chemical Oxidants

The information available on haloalcohol oxidation with chemical oxidants was limited to a few chlorinated and brominated derivatives of ethanol and propanol, but the results were consistent and should apply to the remaining haloalcohols reviewed in this study. The chemical oxidants all converted the alcohols to the corresponding carbonyl group:



The oxidants evaluated include single electron transfer transition metal complexes (e.g., Co^{II} , Ce^{IV} , and Mn^{III}) (Waters and Littler, 1965), metal and halogen oxides (e.g., bromate, chromate, and permanganate) (March, 1968; Banerji, 1973a; Radhakrishnamurti and Behera, 1971; Natarajan and Venkatasubramanian, 1969; 1974), halogens (e.g., Br_2 and Cl_2) (Banerji, 1973b; Myszkowski et al., 1974) and Chloramine-T (Natarajan and Thiagarajan, 1975).

Since water is commonly disinfected by a chemical oxidant, usually chlorine, oxidation of haloalcohols has been considered a potentially important reaction (Morris, 1975). Quantitative data has been published on alcohol and haloalcohol oxidation with a variety of the oxidants. No specific rate data were published for kinetics of haloalcohol oxidation with chlorine. The available kinetic information suggests that the usual concentrations of chlorine applied to water (generally less than 10 ppm) are not sufficient to oxidize chloroalcohols or bromoalcohols at rates which would compete with their degradation by hydrolysis. Table 6 describes some oxidation rates. Based upon this data, it is reasonable to assume that haloalcohol oxidation

Table 6: Observed Oxidation Rates for Various Haloalcohols

Oxidant	Alcohol	Kinetic Data		Conditions of Oxidation	Reference
		Observed Rate Constant, k	Rate Expression ^A		
BrO_3^-	2-Propanol	$36.8 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$	$-\frac{d[\text{Br(V)}]}{dt} = k[\text{Alc}][\text{Br(V)}]$	55°C in 50% aqueous acetic acid + 0.1M H_2SO_4	Natarajan and Venkatasubramanian, 1969
	1,3-Dichloro-2-propanol	$13.5 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$			
CrO_3^-	Ethanol	$1.36 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$	$-\frac{d[\text{Cr(VI)}]}{dt} = k[\text{Alc}][\text{Cr(VI)}]$	35°C in 70% acetone - 30% water + 0.025 M HClO_4	Radhakrishnamurti and Behera, 1971
	2-Chloroethanol	$0.178 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$			
MnO_4^-	Ethanol	$17.4 \times 10^{-2} \text{ min}^{-1} \text{ s}^{-1}$		35°C	Banerji, 1973a
	1-Propanol	$25.0 \times 10^{-2} \text{ min}^{-1} \text{ s}^{-1}$	$-\frac{d(\text{MnO}_4^-)}{dt} = k[\text{Alc}][\text{Mn(VI)}][\text{H}^+]$		
	2-Chloroethanol	$0.166 \times 10^{-2} \text{ min}^{-1} \text{ s}^{-1}$			
	2-Bromoethanol	$0.200 \times 10^{-2} \text{ min}^{-1} \text{ s}^{-1}$			
Br_2	Ethanol	$480 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$	$-\frac{d[\text{Br}_2]}{dt} = k[\text{Alc}][\text{Br}_2]$	35°C in 50% aqueous acetic acid + 0.25 M sodium acetate	Banerji, 1973b
	2-Chloroethanol	$0.86 \times 10^{-4} \text{ min}^{-1} \text{ s}^{-1}$			
Chloramine-T (sodium salt N-chlorotoluene-p-sulfonamide)	2-Butanol	$2.0 \times 10^{-5} \text{ s}^{-1}$ ^a	$-\frac{d[\text{CAT}]}{dt} = k[\text{CAT}]$	55°C in 50% aqueous acetic acid: * 0.2M H_2SO_4 * 1.0M H_2SO_4	Natarajan and Thiagarajan, 1975
	1-3-Dichloro-2-propanol	$0.64 \times 10^{-5} \text{ s}^{-1}$ ^{a*}			

with chlorine will proceed with an apparent bimolecular rate no greater than $10^{-5} \text{ l}^2 \text{M}^{-2} \text{s}^{-1}$ in typical conditions of water treatment (25°C and neutral pH). If so, the haloalcohol oxidation would proceed at an observed rate of less than $10^{-9} \text{ lM}^{-1} \text{s}^{-1}$ with typical chlorine concentration. This estimated rate is less than the observed hydrolysis rates for the chlorinated and brominated alcohols (see above).

Myszkowski and coworkers (1974) examined the aqueous chlorination of several chloroalcohols in a temperature range of 20°C to 60°C. The selected haloalcohols which they studied were 2-chloroethanol, 1-chloro-2-propanol, 3-chloro-1,2-propanediol, 2,3-dichloro-1-propanol, and 1,3-dichloro-2-propanol. The alcohols were oxidized to the corresponding carbonyl compounds by the reaction:



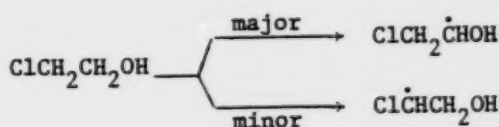
They did not measure rate constants, but did compare rates by means of curves either of chlorocarbonyl compound production versus time or active chlorine oxidant concentration versus time. Their observations corresponded with conclusions set forth above. Substrates with multiple chlorine substitution were oxidized more slowly than analogous monochloroalcohols. Terminal alcohols were oxidized more slowly than secondary alcohols. Also, the oxidation rate increased with increasing temperature.

b. Free-Radical Reactions

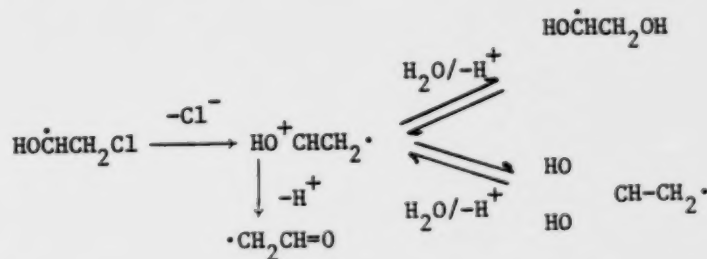
The haloalcohols are expected to degrade in the photochemical smog cycle as the result of free-radical reactions. Some free-radical reactions of 2-bromoethanol and 2-chloroethanol have been studied. The free-radicals react with the haloalcohols to form radicals that are generated by

hydrogen atom abstraction at C_α (carbon bearing the hydroxyl group) or C_β (carbon bearing the halide), or by halogen atom abstraction. By analogy, the other haloalcohols are expected to react by similar pathways.

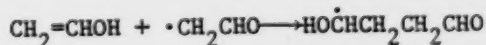
Gilbert and co-workers (1972) investigated the radicals produced in 2-chloroethanol and 2-bromoethanol by atom abstraction with hydroxyl radical. The hydroxyl radicals were generated from titanium(III) - hydrogen peroxide in an aqueous system. The organic free radicals were investigated by means of electron-spin resonance spectrometry (esr). Chloroethanol yielded an esr spectrum containing signals of several radicals. The following radicals were identified: $\cdot\text{CH}(\text{OH})\text{CH}_2\text{OH}$ (a); $\cdot\text{CH}_2\text{CH}_2\text{OH}$ (b); $\cdot\text{CH}(\text{OH})\text{CH}_2\text{CH}_2\text{CHO}$ (c); $\cdot\text{CHClCH}_2\text{OH}$ (d); and $\cdot\text{CH}_2\text{CH}(\text{OH})_2$ (e). Based upon these results Gilbert *et al.* suggested that the radicals initially generated underwent additional radical or ion reactions. Hydrogen abstraction at C_β was minor with respect to abstraction at C_α .



The remaining radicals came from hydrolysis reactions of $\text{ClCH}_2\dot{\text{C}}\text{HOH}$:



and radical reaction with enol:



The distribution of these radicals was strongly pH dependent. While b and c were the major radicals at pH 2, they were not detected at pH 3.6 to 4.2. At the higher pH, e was the major radical. At pH 2 2-bromoethanol yielded products from hydrogen abstraction at C_α ; no $\cdot\text{CHBrCH}_2\text{OH}$ radical was detected. The same proportion of radicals b and c were produced from 2-bromoethanol and 2-chloroethanol.

Anbar and Neta (1967) measured the specific reaction rate constants for 2-chloroethanol and 2-bromoethanol with hydrogen atom, hydroxyl radical, and solvated electron (e_{aq}^-). The radical species were generated by γ -irradiation of aqueous solutions of the alcohols. Specific rates for various reactions are summarized in Table 7. Rate constants indicated that hydroxyl radical abstracted hydrogen (to yield H_2O) more rapidly than atomic hydrogen abstracted hydrogen (to yield H_2). While the rate constant for hydrogen abstraction by hydroxyl radical was about twice as fast for ethanol as for the 2-haloethanols, its abstraction by hydrogen atom was about the same for all three alcohols. Halide abstraction by hydrogen atom was about 100-fold faster from bromoalcohols than from chloroalcohols.

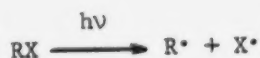
3. Photolysis

No ultraviolet absorption data was found for the haloalcohols (Sadtler Research Laboratory, 1976). Neither the alkyl halides nor alcohols have absorption maxima in the sunlight region (wavelengths above 300 nm). The absorption maxima are probably below 250 nm and therefore, they will absorb very little light above 300 nm (see Subsection I.A.2). No significant environmental photochemistry resulting from direct absorption of light energy is expected.

Table 7. Specific Rate Constants ($\text{lmoles}^{-1}\text{sec}^{-1}$) for
Reactions of Haloalcohols with H , $\cdot\text{OH}$, and
 e_{aq}^- (Adapted from Anbar and Neta, 1967)

$\text{XCH}_2\text{CH}_2\text{OH}$	$(\text{lmoles}^{-1}\text{sec}^{-1})$			
	$k_{\text{OH} + \text{RX}}$	$k_{\text{H} + \text{RX} \rightarrow \text{H}_2}$	$k_{\text{H} + \text{RX} \rightarrow \text{HX}}$	$k_{\text{e}_{\text{aq}}^- + \text{RX}}$
H	1.1×10^9	1.6×10^7	-	10^5
Cl	5.5×10^8	1.5×10^7	1.5×10^6	4.6×10^8
Br	4.6×10^8	1.7×10^7	1.7×10^8	1.6×10^9

Irradiation at lower wavelengths will initiate photochemical reactions. The primary process for alkyl bromides and chlorides consists of homolytic carbon halogen bond breakage to produce alkyl radical and halogen atom (Calvert and Pitts, 1966):



Shortridge and Heicklen (1973) examined the photochemical reactions of 2-bromoethanol in the gas phase. They irradiated systems containing oxygen pressures of 0 to 44 torr and varying, small concentrations of NO (36 to 140 mtorr) or NO₂ (73 to 130 mtorr). They irradiated the system with either 253.7 nm or 228.8 nm light. The primary reaction was the carbon-halide bond cleavage. The resulting alkyl radical then reacted by a chain mechanism. Products included RO₂H, RO₂NO, RO₂NO₂ (where R = HOC₂H₄), HOCH₂CHO, and formaldehyde.

II. Environmental Exposure Factors

A. Production and Consumption

1. Quantities Produced

The approximate annual production volumes of the haloalcohols are listed in Table 8. For the most part, the production volumes were obtained by indirect methods; an explanation of how the quantities were derived is given below.

It should be noted that there was no available import data for most of the haloalcohols.

a. Chloropropanols

The chloropropanols (propylene chlorohydrins) are intermediates in the commercial production of propylene oxide through chlorohydrination of propylene and are not isolated. The two isomers, 1-chloro-2-propanol and 2-chloro-1-propanol, are formed in an approximate ratio of 9:1 (Horsely, 1968). In 1977, 1,897 million lbs of propylene oxide was produced (USITC, 1977 preliminary) of which about 60% was made by the chlorohydrination method (Blackford, 1976a). Assuming an average yield of 95% for chloropropanol conversion to propylene oxide, roughly 1,950 million lbs of chloropropanols were produced as intermediates, of which 1,755 million lbs were 1-chloro-2-propanol and 195 million lbs were 2-chloro-1-propanol. Some refined 1-chloro-2-propanol is also produced domestically, but this amount is small compared to the amount used to manufacture propylene oxide. It is judged that only several thousand pounds of refined 1-chloro-2-propanol is annually made (SRC estimate).

Table 8: Estimated 1977 Annual Production Volumes
of Haloalcohols (SRC Estimates)

<u>Haloalcohol</u>	<u>Annual Production Volume</u>
1-Chloro-2-propanol	1,755 million lbs *
2-Chloro-1-propanol	195 million lbs *
1,2-Dichloro-3-propanol	410 million lbs *
1,3-Dichloro-2-propanol	175 million lbs *
3-Chloro-1,2-propanediol	195 million lbs *
2-Chloroethanol	70-150 million lbs *
2,2,2-Trichloroethanol	Laboratory Amounts Only
2-Bromoethanol	Laboratory Amounts Only
2,3-Dibromo-1-propanol	<10 million lbs
2,2,2-Trifluoroethanol	<0.1 million lbs

* Primarily produced as a non-isolated intermediate.

b. Dichloropropanols

Dichloropropanols (dichlorohydrins) are intermediates in the commercial production of epichlorohydrin. Two isomers, 1,2-dichloro-3-propanol and 1,3-dichloro-2-propanol, are formed in an approximate ratio of 7:3 (Lichtenwalter and Riesser, 1964). In 1973, 345 million lbs of epichlorohydrin were produced (Oosterhof, 1975), which would require about 505 million lbs of dichloropropanol intermediates. Current capacity of industry to make epichlorohydrin is slightly more than 450 million lbs annually (SRI, 1977a). Assuming a modest growth rate for epichlorohydrin from 1973 to the present and assuming that roughly 90% of capacity is currently utilized, then roughly 585 million lbs of dichloropropanol are currently required as intermediates to make epichlorohydrin. Of this, 410 million lbs would be 1,2-dichloro-3-propanol and 175 million lbs would be 1,3-dichloro-2-propanol.

A refined 1,3-dichloro-2-propanol product is also produced but is small relative to the amount consumed as an intermediate in epichlorohydrin production. It is judged that less than one million lbs of the refined 1,3-dichloro-2-propanol are annually produced (SRC estimate).

c. 3-Chloro-1,2-propanediol

3-Chloro-1,2-propanediol (α -monochlorohydrin) is an intermediate in the manufacture of glycerine through the allyl chloride-epichlorohydrin route (Oosterhof, 1976). In 1974, 133 million lbs of glycerine were produced by this route (Oosterhof, 1976), requiring roughly 195 million lbs of 3-chloro-1,2-propanediol intermediate. Since the production of glycerine by the alkyl chloride-epichlorohydrin has remained stable in recent years, the current annual production of 3-chloro-1,2-propanediol should be about the same.

Production of 3-chloro-1,2-propanediol for purposes other than the intermediate use described above is very small by comparison. Less than one million lbs are estimated to be produced for other purposes (SRC estimate).

d. 2-Chloroethanol

Chloroethanol (ethylene chlorohydrin) is produced as an intermediate in the chlorohydrin process used only by Dow for the production of ethylene oxide. In 1975, Dow produced 25 to 50 million lbs of ethylene oxide by this route (Blackford, 1976b), requiring roughly 50 to 100 million lbs of 2-chloroethanol intermediate. The Dow facilities that produce 2-chloroethanol intermediate were shutdown in 1972, and were restarted in 1975 (Blackford, 1976b). Before the 1972 shutdown as much as 500 million lbs of ethylene oxide were made annually through chlorohydrination; current capacity at Dow is estimated at 200-250 million lbs (Blackford, 1976b).

Ethylene oxide can be used to manufacture 2-chloroethanol. According to Blackford (1976b), as much as 20 million lbs of ethylene oxide were consumed in the production of 2-chloroethanol in 1972 and 1974; this would produce roughly 40 million lbs of 2-chloroethanol.

e. 2,3-Dibromo-1-propanol

The main use of dibromopropanol has been in the production of tris(2,3-dibromopropyl) phosphate, commonly called Tris. According to Lande et al. (1976), between 9 to 12 million lbs of Tris were produced in 1975. Production of this amount of Tris would require about 7.5 to 10 million lbs of dibromopropanol. SRI (1976b) estimated the 1976 production of dibromopropanol

to be somewhat greater than 10 million lbs. However, the production of dibromopropanol has fallen dramatically since 1976 due to restrictions upon Tris use (see Subsection II.A.5 for additional discussion). Therefore, current 2,3-dibromo-1-propanol production is definitely less than 10 million lbs. Dibromopropanol production for purposes other than Tris manufacture probably does not total more than one million lbs annually (SRC estimate).

f. 2,2,2-Trifluoroethanol

2,2,2-Trifluoroethanol is produced in commercial quantities, but production volumes are not available from the manufacturer. In 1966, the price of trifluoroethanol was \$7.50/lb (Ferstandig, 1966); the current price is \$8.15/lb. Ferstandig (1966) stated that any significant increase in production would probably reduce its price markedly. Although the current price may be considered somewhat lower than the 1966 price due to the effect of inflation, it is not markedly lower. This observation suggests that current production of trifluoroethanol is not significantly higher than in 1966 since the price has not changed much. Considering the uses and the price of trifluoroethanol, current production is probably less than 0.1 million lbs annually (SRC estimate).

g. Other Haloalcohols

There is no data currently available which would indicate that 2-bromoethanol and 2,2,2-trichloroethanol are produced in any quantities other than laboratory amounts. Production is estimated to be less than 1000 lbs per year.

2. Producers, Production Sites, and Distributors

a. Chloropropanols

1-Chloro-2-propanol and 2-chloro-1-propanol are both intermediates in the production of propylene oxide by chlorohydrination. The companies listed below produce propylene oxide by this method; the chloropropanol capacities are estimated from propylene oxide capacities:

		<u>Chloropropanol Capacity (millions of lbs)</u>
BASF Wyandotte Corp.	Wayandotte, Mich.	300
Dow Chemical	Freeport, TX	1570
	Plaquemine, LA	580
Olin Corp.	Brandenburg, KY	220
		<u>2670</u>

In addition, the following two producers make 1-chloro-2-propanol as a final product (SRI, 1979; EPA, 1979):

Eastman Kodak	Rochester, NY
R.S.A. Corp.	Ardsley, NY

b. Dichloropropanols

1,2-dichloro-3-propanol and 1,3-dichloro-2-propanol are both intermediates in the production of epichlorohydrin. The companies listed below produce epichlorohydrin from the dichloropropanols; the dichloropropanol capacities are estimated from epichlorohydrin capacities:

		<u>Dichloropropanol Capacity (millions of lbs)</u>
Dow Chemical	Freeport, TX	365
Shell Chemical	Houston, TX	250
	Norco, LA	90
		<u>660</u>

In addition, the two following companies produce 1,3-dichloro-2-propanol as a final product (SRI, 1977a; SRI, 1979):

Aceto Chemical	Carlstadt, NJ
Eastman Kodak	Rochester, NY

c. 3-Chloro-1,2-propanediol

3-Chloro-1,2-propanediol is an intermediate in the production of glycerine by the allyl chloride-epichlorohydrin method. The companies listed below produce glycerine by this method; the 3-chloro-1,2-propanediol capacities are estimated from glycerine capacities:

		3-Chloro-1,2-propanediol Capacity (millions of lbs)
Dow Chemical	Freeport, TX	150
Shell Chemical	Deer Park, TX	130
		280

In addition, the following companies make 3-chloro-1,2-propanediol as a final product (SRI, 1979; Environmental Protection Agency, 1979):

Aceto Chemical	Carlstadt, NJ
Dixie Chemical	Bayport, TX
Evans Chemetics	Waterloo, NY
Millmaster Chemical	Berkeley Heights, NJ
Tennessee Eastman Chemical	Kingsport, Tenn.

d. 2-Chloroethanol

Dow Chemical produces 2-chloroethanol as an intermediate in the chlorohydrin method for ethylene oxide production in Freeport, TX. Based on Dow's ethylene oxide capacity by this method (SRI, 1977a), the Freeport plant has the capacity to produce approximately 400 to 500 million lbs of 2-chloroethanol annually.

The following companies also produce 2-chloroethanol

(SRI, 1979; Environmental Protection Agency, 1979):

Union Carbide Corp.	Institute and South Charleston, W.Va.
Thiokol Chemical Div.	Mass Point, MA
Continental Oil Co.	West Lake, LA

e. 2,2,2-Trichloroethanol

The following companies produce 2,2,2-trichloroethanol

(SRI, 1979):

Aldrich Chemical	Milwaukee, WS
R.S.A. Corp.	Ardsley, NY

f. 2-Bromoethanol

2-Bromoethanol is produced in laboratory amounts by

(SRI, 1979; Environmental Protection Agency, 1979):

Aldrich Chemical	Milwaukee, WS
Columbia Organic Chemicals	Columbia, SC
Eastman Kodak	Rochester, NY

g. Dibromopropanol

2,3-Dibromo-1-propanol is produced by the following companies (SRI, 1977a; Environmental Protection Agency, 1979):

Great Lakes Chemical Corp.	El Dorado, AR
Velsicol Chemical Corp.	St. Louis, MO.
Stauffer Chemical Co.	Edison, NJ
Columbia Organic Chemicals	Columbia, SC

h. 2,2,2-Trifluoroethanol

2,2,2-Trifluoroethanol is produced by Halocarbon Products Corporation in Hackensack, NJ (SRI, 1979).

1. Distribution and Importation

The U.S. Census Bureau does not have separate listings for importation of individual haloalcohols. However, it is judged that only small quantities of these compounds, if any, are imported with any consistency (SRC estimate); 2-chloroethanol is an exception. In 1977, between 0.2 and 2 million lbs of 2-chloroethanol were imported (Environmental Protection Agency, 1979).

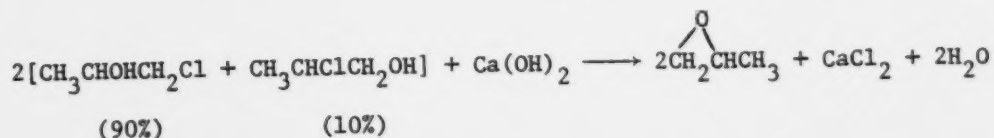
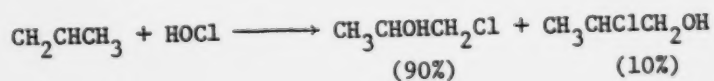
In addition to the manufacturers, the companies listed below are suppliers of the indicated haloalcohols (OPD, 1977; Chemical Week, 1977):

3-chloro-1,2-propanediol:	Howard Hall & Co.	Cos Cob, CN
2-chloroethanol	: Nippon Soda, Co. Ltd.	New York, NY
2,2,2-Trichloroethanol	: Chemical Dynamics Corp. Wall Chemical Corp.	South Plainfield, NJ Westfield, NJ
2,2,2-Trifluoroethanol	: Rhodia, Inc. PCR, Inc. Chemical Dynamics Corp.	Monmouth Jnc, NJ Gainsville, FL South Plainfield, NJ

3. Production Methods and Processes

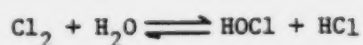
a. Chloropropanols

Most of the chloropropanols produced in the U.S. are consumed as captive intermediates in the production of propylene oxide. The two chloropropanol isomers made during this process, 1-chloro-2-propanol and 2-chloro-1-propanol (formed in approximately 9:1 ratio) are never isolated. The overall reaction of this chlorohydrin method for propylene oxide production can be represented as follows:



The mixture of chloropropanols is commonly called propylene chlorohydrin.

In the commercial production of propylene oxide, propylene, chlorine, and water are fed into a reactor tower where they react under controlled conditions to form propylene chlorohydrin. The process initiates with a preequilibrium during which the chlorine and water react to form hypochlorous and hydrochloric acid



The conditions for the product feed to the tower reaction are chosen so that the propylene chlorohydrin concentration leaving the tower is 3 to 4%, which minimizes by-product formation. The propylene chlorohydrin is then dehydrochlorinated with slaked lime to form propylene oxide (Lowenheim and Moran, 1975). This commercial process is illustrated in Figure 1.

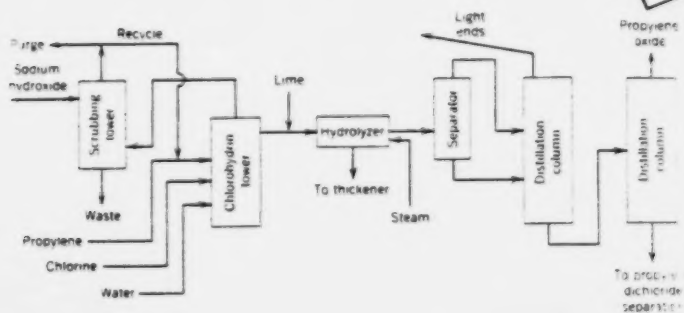
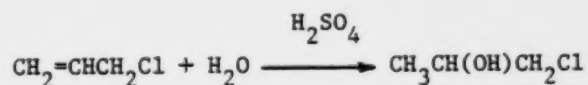


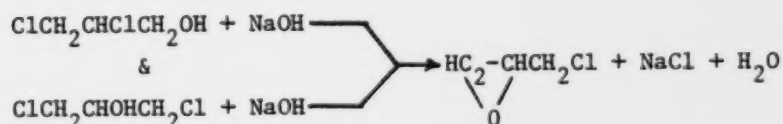
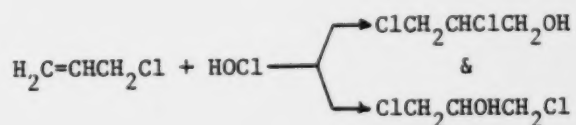
Figure 1. Production of Propylene Oxide through Chloropropanols (Lowenheim and Moran, 1975). Reprinted with permission from John Wiley & Sons, Inc.

1-Chloro-2-propanol, free of the 2-chloro-1-propanol isomer, can be prepared by the acid-catalyzed hydration of allyl chloride (Lichtenwalter and Riesser, 1964):



b. Dichloropropanols

Most of the dichloropropanols produced in the U.S. are intermediates in the manufacture of epichlorohydrin. The two isomers produced by this process, 1,2-dichloro-3-propanol and 1,3-dichloro-2-propanol (formed in a 7:3 ratio) are never isolated (Lichtenwalter and Riesser, 1964). The production of epichlorohydrin proceeds through the following reaction sequence (Oosterhof, 1975):



In the commercial production of epichlorohydrin, propylene and chlorine are fed to a reactor to form allyl chloride which is then fed into another reactor along with chlorine and water. The chlorine and water form

hypochlorous acid (see above) which reacts with the allyl chloride to form the propylene dichlorohydrins (Lowenheim and Moran, 1975). This commercial process is illustrated in Figure 2.

1,3-Dichloro-2-propanol can be obtained in yields of 99.6% by addition of epichlorohydrin to hydrochloric acid (Lichtenwalter and Riesser, 1964).

c. 3-Chloro-1,2-propanediol

Most of the 3-chloro-1,2-propanediol produced in the U.S. is consumed as an intermediate in the production of glycerine by the allyl chloride-epichlorohydrin route and is not isolated. The previous subsection described epichlorohydrin production from the propylene dichlorohydrins. To produce glycerine, the crude epichlorohydrin is hydrolyzed with aqueous sodium hydroxide. Intermediate 3-chloro-1,2-propanediol is produced in the glycerine production as shown by the following reactions (Oosterhof, 1976):



The complete glycerine production route is shown in Figure 3.

Pure 3-chloro-1,2-propanediol can be obtained from the sulfuric acid-catalyzed hydrolysis of epichlorohydrin, or by heating glycerol to 100°C with 2% acetic acid catalyst and adding HCl gas to the mixture (Lichtenwalter and Riesser, 1964).

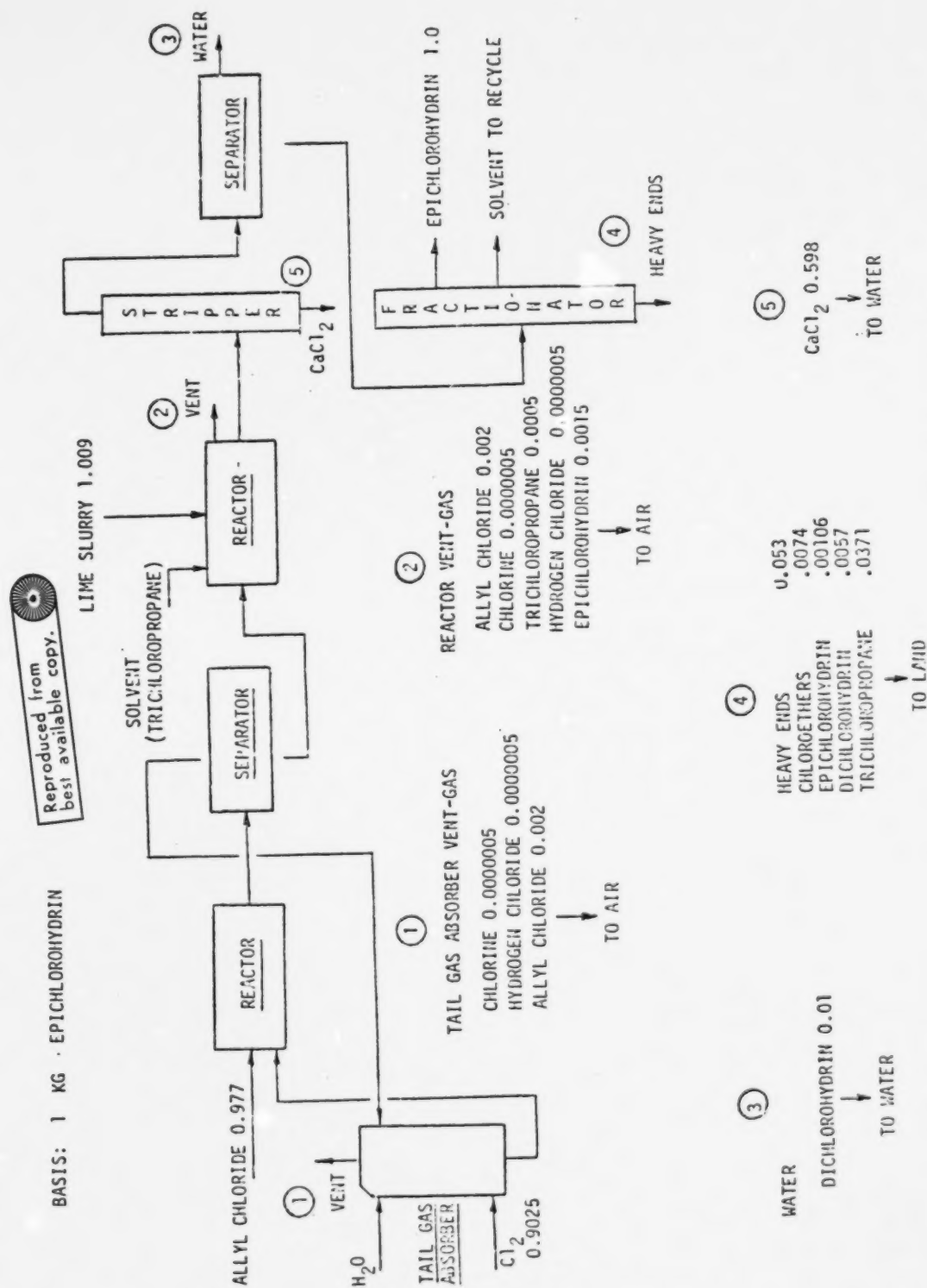


Figure 2. Epichlorohydrin Manufacture (Gruber, 1976)

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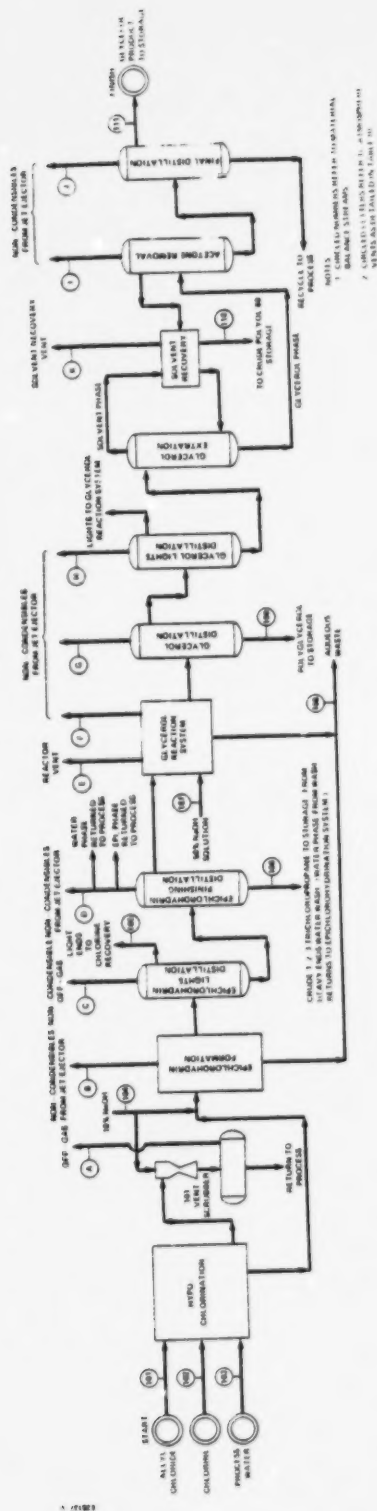


Figure 3. Production of glycerine (glycerol) via epichlorohydrin (Pervier et al., 1974).

d. 2-Chloroethanol

In the past, 2-chloroethanol (ethylene chlorohydrin) has been manufactured commercially by two different processes. Currently, it is produced only as an unisolated intermediate in the manufacture of ethylene oxide through the chlorohydrin process (see Subsection II.A.1.d). Synthesis of ethylene oxide begins with conversion of ethylene to 2-chloroethanol with hypochlorous acid (see above), and the resulting chlorohydrin is dehydrochlorinated with slaked lime. The reaction can be represented as follows:



The commercial process is illustrated in Figure 4.

A second production route to 2-chloroethanol is not currently in commercial operation. In this process 2-chloroethanol is manufactured by reacting ethylene oxide with HCl or MgCl_2 . Union Carbide produced 2-chloroethanol in this way in 1972 and 1974 (Blackford, 1976b).

e. 2,2,2-Trichloroethanol

2,2,2-Trichloroethanol is not produced in commercial amounts, but rather is made only in laboratory quantities (<1000 lbs per year). It can be synthesized by at least two routes. One method consists of reduction of trichloroacetic acid or a derivative (ester or acyl chloride)

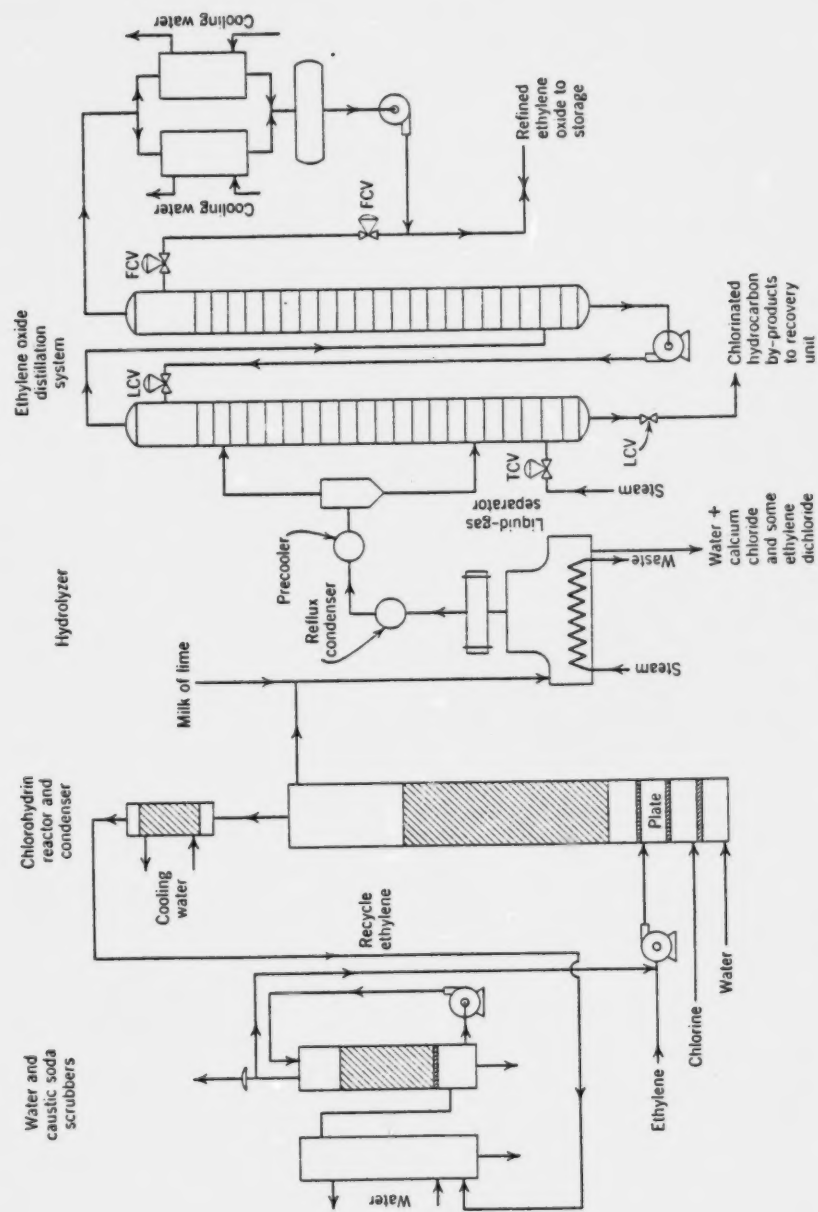
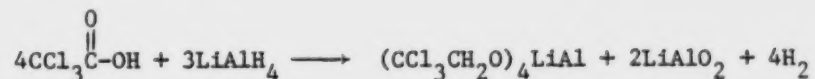


Figure 4. Chlorohydrin process for manufacturing ethylene oxide (Schultze, 1965).
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with lithium aluminum hydride (Windholz, 1976). This synthesis, which is similar to commercial production of trifluoroethanol, may be represented by the following reaction (Royals, 1954):



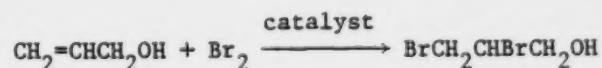
Manufacture of 2,2,2-trichloroethanol can also be accomplished by reducing chloral hydrate with an amine borane (Chamberlain and Schechter, 1959) or by reducing chloral with aluminum ethylate (Turi, 1966).

f. 2-Bromoethanol

2-Bromoethanol is not produced in commercial amounts, but is made only in laboratory quantities (<1000 lbs per year). 2-Bromoethanol can be synthesized by the action of hydrobromic acid with ethylene oxide (Windholz, 1976); a similar synthesis of 2-bromoethanol involves reaction of dry HBr and ethylene oxide in liquid SO_2 (Gebhart, 1949).

g. 2,3-Dibromo-1-propanol

2,3-Dibromo-1-propanol is produced commercially by reacting allyl alcohol with bromine. The reaction may be represented as follows:



One patent describes the synthesis as follows (Thomas and Levek, 1971):

"..... 1.01 moles allyl alc. and 1 mole Br were added to 60% aq. LiBr at 35-40°, the org. phase sepd., 60% aq. LiBr solu. added, the entire procedure repeated up to conversion of 21 moles Br, and the combined org. phases washed to give 2,3-dibromopropanol of 99.9% purity." The process may be illustrated

by the simple flow diagram shown in Figure 5. Clemons and Overbeek (1966) indicated that the product yield can be upgraded by recycling the reaction products.

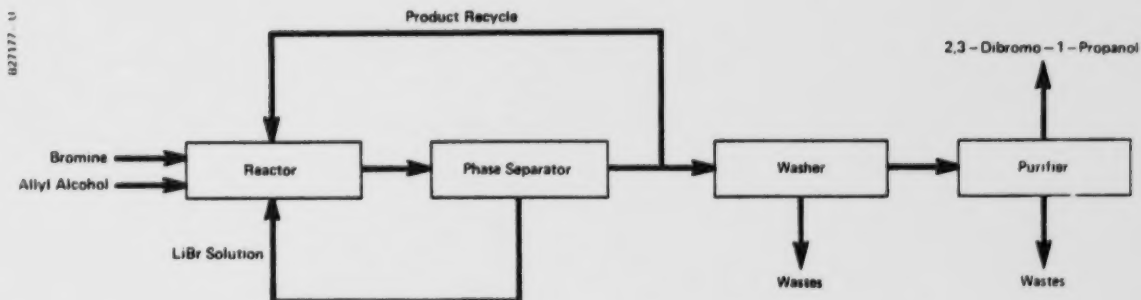


Figure 5. Production of 2,3-Dibromo-1-propanol (adapted from Thomas and Levek, 1971; Clemons and Overbeek, 1966)

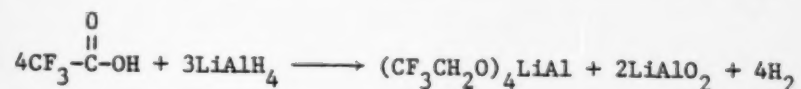
In the past, most 2,3-dibromo-1-propanol was consumed as an unisolated intermediate in the manufacture of Tris (see Subsection II.A.1.e). Now, however, since the production of Tris has been severely curtailed due to its restricted use for clothing flame retardancy, most dibromopropanol is isolated as a final product.

h. 2,2,2-Trifluorethanol

2,2,2-Trifluorethanol was first prepared by the reduction of trifluoroacetic anhydride. Other syntheses used alternative reduction methods: trifluoroacetamide with a platinum catalyst; trifluoroacetic esters

with LiAlH_4 , and trifluoroacetic acid with LiAlH_4 (Ferstandig, 1966). It can also be made from trifluoroethyl chloride by acetolysis followed by hydrolysis (Ferstandig, 1966). More recent production methods involve catalytic hydrogenation of CF_3COCl using $\text{Pd}/\text{Al}_2\text{O}_3$ (Wolownik, 1976) and hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate (Agnello and Cunningham, 1967).

The production of 2,2,2-trifluoroethanol by reduction of trifluoroacetic acid with LiAlH_4 can be represented as follows (Royals, 1954):



The production process would involve the introduction of trifluoroacetic acid into a reactor containing excess lithium aluminum hydride and refluxing the acid until the reaction is as complete as possible. The metal alkoxide would be hydrolyzed and the excess lithium aluminum hydride would be decomposed with water ($\text{LiAlH}_4 + 2\text{H}_2\text{O} \longrightarrow \text{LiAlO}_2 + 4\text{H}_2$). The 2,2,2-trifluoroethanol is then obtained by fractionation. This production process is illustrated in Figure 6 below.

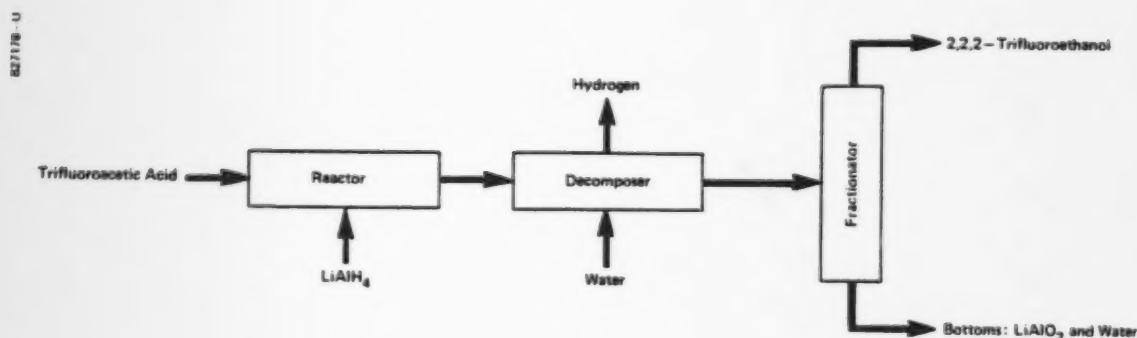


Figure 6. Production of 2,2,2-Trifluoroethanol through Reduction with LiAlH_4 . (adapted from Royals, 1954)

4. Market Prices

Current market prices for the haloalcohols are listed in Table 9. The quoted prices apply to the largest quantity available from the manufacturer.

5. Market Trends

a. Chloropropanols

Growth of chloropropanol production is directly dependent upon growth of propylene oxide production through the chlorohydrin process. The propylene oxide market grew at a rate of about 12% per year from 1965 to 1976; it is projected that growth will average 10% per year to 1980 (Chemical Profiles, 1976). A corresponding growth rate can be expected for the chloropropanols, provided the percentage of propylene oxide manufactured by the chlorohydrin process is not significantly altered.

b. Dichloropropanols

Overall production growth of the dichloropropanols is directly dependent upon growth of epichlorohydrin production since their primary consumption is as intermediates in this process (see Section II.A.1.b). Oosterhof (1975) has projected that the market for crude epichlorohydrin will grow at a rate of 2% to 3% per year while the market for refined epichlorohydrin will grow at a rate of 6% to 7% per year. A corresponding growth rate can be expected for the dichloropropanols produced as intermediates.

Growth rates for the 1,3-dichloro-2-propanol produced as a final product are not available. However, this market is only a fraction of the volume of the intermediate production.

Table 9: 1977 Market Prices for Haloalcohols
(Various Personal Contacts with Manufacturers)

<u>Haloalcohol</u>	<u>Price</u>
1-Chloro-2-propanol	\$55-113.60/kg (largest available quantities)
1,3-Dichloro-2-propanol	\$1.75/lb (bulk)
3-Chloro-1,2-propanediol	\$1.10/lb (bulk)
2,2,2-Trichloroethanol	\$270/10 kg
2-Bromoethanol	\$11.20/100 grams
2,3-Dibromo-1-propanol	\$0.67/lb (bulk)
2,2,2-Trifluoroethanol	\$8.15/lb (bulk)

c. 3-Chloro-1,2-propanediol

Overall production growth for 3-chloro-1,2-propanediol is directly dependent upon growth of glycerine made through the allyl chloride-epichlorohydrin process, because 3-chloro-1,2-propanediol is formed as an intermediate during this process. Oosterhof (1976) has projected that the glycerine production will grow at a low rate of only 2% to 3% per year. A corresponding growth rate can be expected for the 3-chloro-1,2-propanediol produced as an intermediate.

Growth rates for the 3-chloro-1,2-propanediol produced as a final product are not available. However, this market is only a fraction of the volume of the intermediate production.

d. 2-Chloroethanol

2-Chloroethanol is produced as an intermediate in ethylene oxide production through chlorohydrination. Production of ethylene oxide through chlorohydrination has been somewhat unstable in recent years. Listed below are the annual amounts of ethylene oxide (in million lbs) made by this route from 1965 to 1975 (Blackford, 1976b):

1975	25-50	1969	361
1974	0	1968	310
1973	0	1967	358
1972	50	1966	491
1971	205	1965	482
1970	363		

In 1972, Dow Chemical terminated production of ethylene oxide by chlorohydrination. In 1975, Dow converted between 200 to 250 million lbs of annual chlorohydrination process capacity from propylene oxide manufacture to ethylene oxide manufacture (Blackford, 1976b). If future production of ethylene oxide

through chlorohydrination increases to a substantial percentage of annual capacity, production of 2-chloroethanol would increase correspondingly.

It is also feasible to manufacture 2-chloroethanol from ethylene oxide on a commercial scale. Blackford (1976b) estimated that in 1972 and 1974 about 20 million lbs of ethylene oxide were consumed in 2-chloroethanol production. Union Carbide, the producer at that time, is no longer making 2-chloroethanol. Exactly what has happened to this market for 2-chloroethanol is not certain. It is possible that either imports or Dow Chemical has taken over the market. Projections of growth rates are not possible from the limited data.

e. 2,3-Dibromo-1-propanol

The following market trends have been indicated for 2,3-dibromo-1-propanol (SRI, 1977b).

"Until recent years, it is believed that practically all 2,3-dibromo-1-propanol was used as an intermediate for the manufacture of the flame retardant, tris(2,3-dibromopropyl) phosphate (so-called TRIS). More recently it is believed to have found some use as an intermediate for reactive flame retardants (e.g., dibromopropyl acrylate and methacrylate) and as a reactive flame retardant itself."

"Although TRIS has found some use as a flame retardant in a variety of other applications, it is believed that its major application since 1973 has been in the treatment of fabrics for use in infants' and children's sleepwear. As a result of concern about the mutagenic and carcinogenic properties of TRIS, the manufacturers of this sleepwear stopped using TRIS-treated fabrics in January 1977 and the Consumer Product Safety Commission banned the

sale of TRIS-treated sleepwear in April 1977. Since that time, users of TRIS for other flame retarding purposes have announced decisions to stop using it. Consequently, it seems very likely the total U.S. production of 2,3-dibromo-1-propanol has already decreased dramatically and will continue to do so. Its use in reactive flame retardants for such products as polyurethane foams, which is believed to be still in the development stage, is likely to be adversely affected by the fact that 2,3-dibromo-1-propanol itself has been found to be mutagenic also."

f. 2,2,2-Trifluoroethanol

As explained in Section II.A.1.f., production of trifluoroethanol is not considered to be significantly greater at present than in the mid-1960s. Future projections are not available; however, the historical trend would indicate a stable market in the near future.

B. Uses of Haloalcohols

1. Uses and Their Chemistry

a. Chloropropanols

Nearly all of the two isomers of chloropropanol produced domestically in commercial quantities (1-chloro-2-propanol and 2-chloro-1-propanol) are consumed captively as intermediates in the production of propylene oxide. The production methods and chemistry of these uses are discussed in Section II.A.3.a.

The 1-chloro-2-propanol isomer is produced in small commercial amounts; perhaps several thousand lbs per year. Its uses are not available from the manufacturers. However, a survey of patent literature indicates that many derivatives of 1-chloro-2-propanol have potential use in

nematocides, herbicides, and insecticides. Other possible uses include rubber stabilizers, lubricants, and general use in organic syntheses.

b. Dichloropropanols

Most of the two isomers of dichloropropanol produced domestically in commercial quantities (1,3-dichloro-2-propanol and 1,2-dichloro-3-propanol) are consumed captively as intermediates in the production of epichlorohydrin. The production method and chemistry are discussed in Section II.A.3.b.

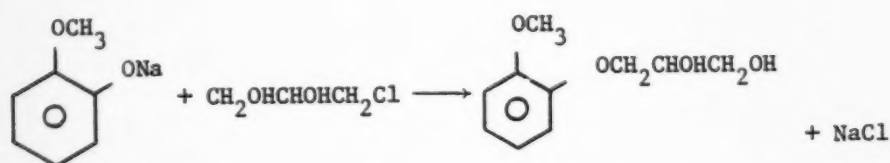
1,3-Dichloro-2-propanol is produced in commercial quantities as a refined, industrial product, although its production is much smaller than the quantity produced as an intermediate. Its major use is for metal cleaning and plating. According to the principal manufacturer of 1,3-dichloro-2-propanol (refined), the product is sold to a large number of solvent blenders who mix the dichloropropanol into many solvent formulations, most of which are destined for metal cleaning and plating applications.

1,3-Dichloro-2-propanol has minor applications in textile finishing and permanent wave fixing (Lichtenwalter and Riesser, 1964), in manufacture of photographic and Zappon lacquer, in celluloid cement, in binders for water colors, in resin and cellulose solvents, and in general organic syntheses (Windholz, 1976; Rose and Rose, 1956).

c. 3-Chloro-1,2-propanediol

Most of the 3-chloro-1,2-propanediol produced domestically is captively consumed as an intermediate in the production of glycerine through the allyl chloride-epichlorohydrin method. This production method and chemistry are discussed in Section II.A.3.c.

3-Chloro-1,2-propanediol is also marketed as a final product, although in much smaller quantities than that consumed as an intermediate. One of the more important uses is in the preparation of glyceryl guaiacolate. 3-Chloro-1,2-propanediol is reacted with sodium guaiacolate to make guaiacol glyceryl ether (glyceryl guaiacolate), which is an ingredient of commercial cough remedies and expectorants. The glyceryl guaiacolate reaction may be represented by the following:



Glyceryl guaiacolate is manufactured by six American manufacturers (SRI, 1977a): Arsynco, Inc. (Carlstadt, NJ); MWM Chemical Corp. (Plainview, NY); S.B. Penick (Montville, NJ); Ganes Chem. Labs. (Pennsville, NJ); Hexagon Labs (Bronx, NY); and Millmaster Chem. (Berkeley Heights, NJ).

3-Chloro-1,2-propanediol is also a reactant in the chemical syntheses of other glyceryl derivatives which are consumed in plasticizers and in dyes (Lichtenwalter and Riesser, 1964). Minor uses of 3-chloro-1,2-propanediol include applications for the lowering of the freezing point of dynamite (Windholz, 1976) and solvent for acetylcellulose, glyceryl phthalate, resins, and gums (Rose and Rose, 1956).

3-Chloro-1,2-propanediol is also used as the active ingredient in a new rodenticide called Epibloc[®] produced by Gametrics Limited of Sausalito, California. This rodenticide is sold only to government agencies and to individuals qualified in rat control.

d. 2-Chloroethanol

Most of the 2-chloroethanol currently produced in the United States is captively consumed as an intermediate in the production of ethylene oxide by the Dow Chemical Company. This use of 2-chloroethanol is discussed in Section II.A.3.d.

2-Chloroethanol is also an intermediate in the production of several other chemicals, including indigo and dichloroethyl formal, an intermediate for polysulfide elastomers (Blackford, 1976b). Thiodiethylene glycol prepared from 2-chloroethanol is useful in textile printing as a general solvent and hygroscopic agent for dye pastes and as an antioxidant for vat, basic, and acid dyes (Lichtenwalter and Riesser, 1964). 2,2'-Dichlorodiethyl ether, another 2-chloroethanol derivative, is utilized in the manufacture of morpholine and in the Chlorex process as an extractive solvent for refining of lubricating oils. However, these uses are not considered to be commercially important any more, although the ether has been used in commercial synthesis of surfactants (Durkin et al., 1975). In addition, 2-chloroethanol derivatives have been consumed in insecticides, herbicides, anesthetics, growth modifiers, and therapeutics agents (Lichtenwalter and Riesser, 1964).

e. 2,2,2-Trichloroethanol

2,2,2-Trichloroethanol is manufactured in relatively small amounts. Some trichloroethanol is consumed in pharmaceuticals. Trichloroethanol, by itself, is a powerful hypnotic that is sometimes used in control of motion sickness, but this application is now limited since it also causes respiratory depression (Turi, 1966). A recently prepared hypnotic agent is derived by shaking an equivalent of hexamethylene tetramine with three

equivalents of trichloroethanol in water until crystals are formed; this material yields a complex with the formula $[\text{CCl}_3\text{CH}_2\text{OH}]_3 \cdot (\text{CH}_2)_6\text{N}_4$ (Turi, 1966).

f. 2-Bromoethanol

2-Bromoethanol is currently not produced in commercial quantities. A survey of patent literature indicates that 2-bromoethanol has potential applications in pesticides, for preparing pesticide intermediates, in preparing fire-resistant intermediates, in photographic emulsions, as a general solvent, and in preparing intermediates for other chemical synthesis.

g. 2,3-Dibromo-1-propanol

The major use of 2,3-dibromo-1-propanol has been in the production of tris(2,3-dibromopropyl)phosphate, a flame retardant which is commonly known as Tris. Tris is commercially produced by the reaction of dibromopropanol and phosphorus oxychloride as shown:



A base is required to neutralize the HCl produced. As explained in Section II.A.5.g., Tris production has fallen dramatically. At this time other uses of dibromopropanol might be more important commercially than Tris production.

2,3-Dibromo-1-propanol is employed as a reactive flame retardant ingredient for the production of flexible polyurethane foam with reduced combustion properties and is also an important raw material for the production of useful retardant additives (Velsicol Chemical Co., 1977). Two of the more important retardant additives are thought to be dibromopropylacrylate and the methacrylate analog (SRI, 1977b).

Dibromopropanol has potential use as an intermediate in production of pesticidal and pharmaceutical chemicals (Great Lakes, 1972).

h. 2,2,2-Trifluoroethanol

A bulletin from Halocarbon Products (1967) describes the following uses for 2,2,2-trifluoroethanol:

"Trifluoroethanol because of its hydrogen bonding ability and ionization constant is an excellent solvent for ionic reactions, conductometric titrations and the like. Small amounts of water (1-5%) enhance the properties desired for these types of uses.

The room temperature solubility of nylons in trifluoroethanol lends itself to many unusual applications. For example, if a loop of dry nylon rope is dipped in the alcohol for a few seconds it immediately becomes stiff upon removal. After evaporation of the trifluoroethanol the stiff section is permanently sealed and can be cut to give nonfraying ends with shoelace-like tips. Using a hot air blower the ends of tightly braided 1/4" line can be processed in about 30 seconds. Similarly ordinary knots made with nylon monofilament can be permanently sealed with trifluoroethanol. Under abnormally high humidity conditions a high moisture content in the nylon can interfere with the sealing process.

Nylon solutions in the trifluoroethanol can be used as vehicles for adhesives, pigments, metal powders or dyes. These mixtures yield nylon toughened adhesives or, upon evaporation, deposit tough surface coatings."

Trifluoroethanol derivatives have other potential applications in a number of fields. Often the trifluoroethoxy group is profoundly different from the ethoxy group. For example, hexafluorodiethyl ether is a convulsant drug (Indoklon) used in place of electric shock therapy while its analog, diethyl ether, is an anesthetic. Trifluoroethyl vinyl ether is marketed as the low flammability anesthetic "Fluoromar," which is made by the Ohio Chemical and Surgical Equipment Co. of Madison, Wisconsin. Various polymers and copolymers of trifluoroethanol derivatives have been prepared. A trifluoroethyl substituted dye has a different color from the related ethyl dye and is usually

A new procedure for direct propylene oxidation to form propylene oxide using hydrogen peroxide has recently been reported (Anon., 1978a). The method, which was developed by Products Chimique Ugine Kuhlman (PCUK) has only been partially described. Propylene in an unspecified solvent is oxidized with the hydrogen peroxide in the presence of a metal catalyst. A spokesman for PCUK described metaboric acid as a catalyst component, but did not detail the catalyst composition or reaction conditions. The epoxidation selectivity was reported as being on the order of 95%.

b. Dichloropropanols

1,3-Dichloro-2-propanol and 1,2-dichloro-3-propanol are primarily produced as intermediates in epichlorohydrin production. An alternative to this major use of dichloropropanols would be the production of epichlorohydrin by a route which does not require dichloropropanol intermediates. Such an alternative, commercially competitive route does not exist at present and it is uncertain whether such a route will be available in the future. Phillips and Starcher (1957) patented a process by which epichlorohydrin can be produced from allyl chloride by oxidation with peracids, but no information is available to describe its commercial status.

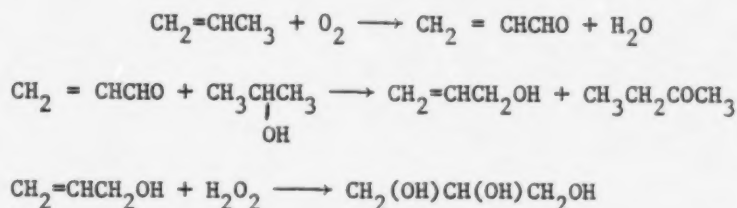
Most of the refined 1,3-dichloro-2-propanol produced in commercial quantities is consumed in solvents blended for metal cleaning and plating. The exact need of this isomer in the solvent blends is not clear. Other chlorinated compounds or solvents might be acceptable alternatives to these applications.

c. 3-Chloro-1,2-propanediol

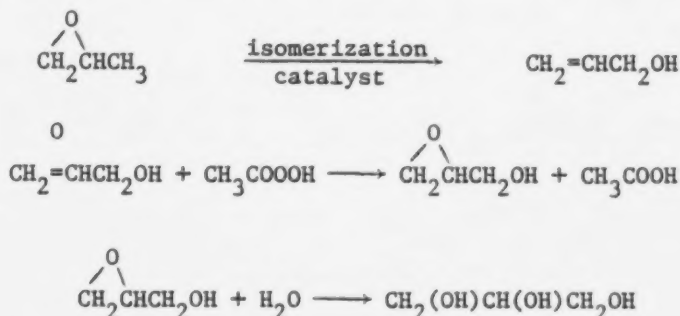
3-Chloro-1,2-propanediol is primarily produced as an

intermediate in glycerine production via the allyl chloride-epichlorohydrin route. An alternative to this use is glycerine production by different commercial methods; such commercial methods include the acrolein-allyl alcohol route and the allyl alcohol-peracetic acid-glycidol route. As of 1976, 71% of industrial capacity to make synthetic glycerine was based on the allyl chloride-epichlorohydrin route, 16% was based on the acrolein-allyl alcohol route, and 13% was based on the glycidol route (Oosterhof, 1976).

The acrolein-allyl alcohol method consists of the following three steps (Oosterhof, 1976; Shell Oil Co., 1979-personnel communication):



The allyl alcohol-peracetic acid-glycidol method includes the following three steps (Oosterhof, 1976):

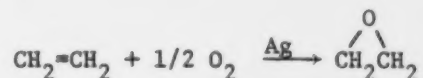


3-Chloro-1,2-propanediol is used in small quantities as the active ingredient in a rodenticide. Alternative, commercial rodenticides include ANTU (α -naphthylthiourea) and Warfarin.

d. 2-Chloroethanol

Currently, 2-chloroethanol is primarily produced as an intermediate in ethylene oxide production via the chlorohydrin process. An alternative to this major use is the production of ethylene oxide by the direct oxidation of ethylene. In 1975 about 99% of the ethylene oxide manufactured was made by direct oxidation while only 1% was made by chlorohydrination (Blackford, 1976b).

The direct oxidation of ethylene to ethylene oxide can be represented by the following reaction:



This process eliminates the disposal problems created by the chlorinated by-products produced via chlorohydrination.

e. 2,3-Dibromo-1-propanol

At present, 2,3-dibromo-1-propanol is mainly used as a flame retardant. Other organic chemicals which can be used for this purpose include phosphate esters and alternative brominated substrates such as isodecyl diphenyl phosphite and hexabromocyclododecane (Sanders, 1978), dibromobutenediol, dibromoneopentyl glycol and tribromoneopentyl alcohol (Levek and Williams, 1975).

Currently, one commercial use of 2,3-dibromo-2-propanol is the synthesis of the flame retardant dibromopropyl acrylate. Flame retardants which have the same use as dibromopropyl acrylate include vinyl bromide, vinylidene chlorobromide, and epibromohydrin (Levek and Williams, 1975).

f. Trifluoroethanol

Trifluoroethanol appears to be fairly unique in its commercial applications, especially in synthesis reactions. Its use to stiffen the ends of nylon rope can probably be imitated by plastic bands as found on shoe laces but the utility of this alternative is not clear.

C. Environmental Contamination Potential

1. General

Release of haloalcohols to the environment is poorly defined. Most of the haloalcohols are consumed as intermediates soon after production and receive little handling other than transfer between process units. Very little information was available which described their loss to the environment as the result of fugitive emissions, venting, or disposal. Because the amount of haloalcohol annually produced is so large, even a low percentage of loss would represent a large environmental emission. The evidence at hand suggests that while the atmospheric emissions during production and consumption as an intermediate are very low, some wastes destined for disposal with little or no treatment could contain residual haloalcohol. Disposal appears to be the greatest hazard. To facilitate the following discussions of the problems of release, haloalcohols consumed as a reaction intermediate are discussed along with haloalcohols manufactured as a final product.

Because most haloalcohols are directly used, emissions as the result of transport and storage can only occur from a relatively small fraction of the annual production.

2. From Production

Very limited information was available which described emissions

during haloalcohol production. Virtually no information was available for environmental loss during the production of commercial, refined haloalcohols. Some information was available for emissions within production processes for individual epoxides, epichlorohydrin and glycerine in which chloroalcohols were intermediates. No haloalcohol was reported among the intermediates, solvents, or products emitted during the actual processing, but they were observed among disposed wastes (see Section II.C.4).

a. Chloropropanols

Almost all chloropropanols are consumed as captive intermediates in propylene oxide manufacture. No information was available on release during production or use. Release seems associated with liquid waste effluent (see Section II.C.4.a).

b. Dichloropropanols

Dichloropropanol is primarily produced and consumed as an intermediate in epichlorohydrin production. Atmospheric losses of dichloropropanols from manufacturing plants are considered insignificant (Pervier et al., 1974). The major source of release would appear to be the waste water effluent and heavy ends destined for solid waste disposal (see Section II.C.4.b) (Gruber, 1976; Pervier et al., 1974).

c. 3-Chloro-1,2-propanediol

Environmental release of 3-chloro-1,2-propanediol intermediate produced in glycerine manufacture as the result of epichlorohydrin hydrolysis is associated with disposal of still pot residues (see Section II.C.4.c). The 3-chloro-1,2-propanediol produced as an intermediate in glycerine

manufacture is generated and consumed within a batch process kettle, so it has little chance for escape (Pervier et al., 1974).

Refining of 3-chloro-1,2-propanediol for marketing as a pure material has potential for emissions from process equipment such as vents, distillation columns and reactors. No specific information was available.

d. 2-Chloroethanol

Potential emissions of 2-chloroethanol are probably similar to those of the chloropropanols, since both are produced and consumed by similar chemical process plants. The emissions are primarily associated with waste disposal (see Section II.C.4.d).

e. 2,3-Dibromo-1-propanol

No specific monitoring data or other information is available on losses of 2,3-dibromo-1-propanol from production. In the production of Tris (see Section II.A.1.e), the dibromopropanol is formed in a batch kettle, purified by washing, and then consumed without isolation. Chances of emission are probably highest during product purification stage and kettle transfers or from waste effluent disposal.

f. Other haloalcohols

No information was available for emissions of 2-bromoethanol, 2,2,2-trichloroethanol, or 2,2,2-trifluoroethanol during their production. These chemicals have limited annual production and no specific details on engineering aspects were available. They are probably manufactured by batch processes in reaction kettles and purified by fractionation. The greatest source for release would appear to be from emissions during the

purification stage and from wastes from kettle and equipment washing and still bottoms (see Section II.C.4).

3. From Transport and Storage

The bulk of the haloalcohols produced in the United States are formed as intermediates during manufacture of such compounds as ethylene oxide, propylene oxide, epichlorohydrin, or glycerine. During these processes, the haloalcohols are neither isolated from the system nor stored. Therefore, the potential for contamination from transport and storage does not apply.

The haloalcohols that are transported in product form are usually shipped in special drums, barrels, or tankers. Barring highway or railway accidents, the potential for contamination is probably small.

The haloalcohol discharged to the environment would consist primarily of vapor loss during transfer to and from containers, and venting of any storage facilities or transport tankers. No quantitative information is available on these various vapor losses.

4. From Use

Most haloalcohols are consumed without isolation as chemical synthesis intermediates. The potential discharge for these reaction intermediates was discussed in Section II.C.2. Potential release from other uses of the haloalcohols to the environment are discussed below.

1,3-Dichloro-2-propanol is blended into solvents which are consumed for metal plating and cleaning. No specific information was available on the cleaning procedure with the dichloropropanol solvent blend

(Schwartzkopf, 1967). Atmospheric emissions could result from solvent evaporation off the metal surface, from solvent evaporation from treatment baths, or from solvent disposal.

2,3-Dibromo-1-propanol is used as a flame retardant, especially in polyurethane foams. For the most part, the dibromopropanol is adequately bound into the urethane matrix. However, it may be possible that small concentrations of the dibromopropanol could diffuse out under abnormal circumstances.

Uses of other haloalcohols as solvents (trifluoroethanol, bromoethanol, etc.) have potential for atmospheric release from evaporation. No information was available which described the quantities used as solvent, pollution controls to prevent atmospheric emission from solvent evaporation, or evaporation rates.

Dibromopropanol could potentially be lost to the environment from fabrics and other materials treated with Tris. Some Tris, lost when treated fabrics are laundered, could hydrolyze in alkaline conditions to yield dibromopropanol (Lande et al., 1976). No quantitative information was available from which the potential importance of this pathway could be estimated. Since Tris is being phased out as a fire retardant for fabric, the potential for release will be reduced.

5. From Disposal

Since most haloalcohols produced each year are consumed as chemical intermediates, only a small fraction of the total production will require disposal. The waste streams potentially containing haloalcohols include those generated in all processes where haloalcohols are produced or used as intermediates.

a. Chloropropanols

The major potential for chloropropanol release to the environment from propylene oxide manufacture via chlorohydrination is in waste water effluents. This chlorohydrin process generates about 60 tons of waste water per ton of propylene oxide (Anon., 1978b). The waste water effluent is unsuitable for direct disposal into natural drainage and will not be accepted in municipal sewage systems without expensive pretreatment (Hancock, 1973). While the waste water's primary contaminant is calcium chloride, it will normally contain small amounts of the chloropropanols. Insufficient monitoring data was available to estimate the chloropropanol concentration within these effluents. In 1977, the production of about 570,000 tons of propylene oxide via chlorohydrination were estimated to produce about 34 million tons of waste waters. Even a small concentration of chloropropanol in these effluents could therefore release significant total amounts of chloropropanols to the environment.

Recently, a new treatment was proposed to resolve the water effluent disposal problem (Anon., 1978b). The C-E Lummus Company demonstrated on a laboratory scale that the calcium chloride (or sodium chloride) brine solution can be fed to an electrolytic diaphragm cell to regenerate chlorine gas and caustic, which could be recycled back to the chlorohydrination process. Although not yet tested under production conditions, this waste treatment method appears to be commercially feasible.

Organic residues in heavy ends from product fractionation could possibly contain chloropropanols. These residues would most likely be disposed by landfills. Monitoring information has identified some haloalcohols in landfill leachate (see Section II.E), which supports this suggestion. No information was available on the haloalcohol content of the residuals.

b. Dichloropropanols

Dichloropropanols (dichlorohydrins) are by-products from the epichlorohydrin manufacturing process in two places (refer to Figure 2 in Section II.A.3.b.). They are released in waste water effluents and as a constituent in the heavy ends from the fractionator. It has been estimated that the total production of epichlorohydrin in 1973 was about 345 million lbs (Oosterhof, 1975). Growth projections would indicate that current epichlorohydrin production is roughly 400 million lbs. (180 million kg). Utilizing this production figure and the monitoring data on Figure 2, the quantity of dichloropropanols annually emitted in waste waters would be about 4 million lbs and the quantity in the heavy ends would be about 2.3 million lbs.

The waste water effluents containing dichloropropanols are treated in on-site facilities; treatment efficiency with respect to dichloropropanols is not available. The heavy liquid ends are stored in large steel tanks at the plant site (Gruber, 1976). Heavy end wastes of this kind can be effectively destroyed by incineration with proper control to eliminate air pollution (Gruber, 1976). The only monitoring information was identification of dichloropropanols in waste water effluent from a chemical plant (Shackelford and Keith, 1976) and in barrels of chemical waste dumped at sea (Greve, 1971) (see Section II.E.).

c. 3-Chloro-1,2-propanediol

No information was available concerning 3-chloro-1,2-propanediol disposal. Pervier and coworkers (1974) described waste streams from glycerol production via epichlorohydrin hydrolysis with aqueous alkali. Since chloropropanediol was not included among the components, it appears that

it is not present in significant quantities. Other possible sources are residues from fractionation processes used to isolate and purify commercial chloropropanediol.

d. 2-Chloroethanol

The potential for 2-chloroethanol residues from the production of ethylene oxide via chlorohydrination is probably quite similar to the potential residues for chloropropanols from the propylene oxide manufacture discussed above. Waste water effluent might be the major disposal problem. Waste water at a Russian ethylene oxide plant had the following content of various chemicals (Antipina, 1957): 0.7-4.8 g/l ethylene glycol; 0.01-0.45 g/l ethylene chlorohydrin (2-chloroethanol); 32-48 g/l CaCl_2 ; 0.9-1.4 g/l Ca(OH)_2 , and traces of acetaldehyde. These data appear to be effluent concentrations before discharge; no information on the composition of the discharged waste was found. The total amounts of 2-chloroethanol released in waste water effluents could be significant. Information was not available on either water waste quantities or on-site treatment efficiency with respect to 2-chloroethanol reduction. The only monitoring information consisted of identification of 2-chloroethanol in industrial waste-water effluents (Shackelford and Keith, 1976) (see Section II.E). 2-Chloroethanol is also present in distillation column bottoms obtained during the ethylene chlorohydrination process for ethylene oxide (Aries et al., 1950). Although these bottoms can probably be incinerated (see Section II.C.5.b) it is possible that still bottoms are disposed by landfill (see Section II.E).

e. 2,3-Dibromo-1-propanol

Generation of 2,3-dibromo-1-propanol wastes should follow a pattern similar to the wastes from other halopropanols consumed as reaction

intermediates. Dibromopropanol has been identified as a constituent of wastewater effluent, in landfill leachate, and in well water apparently polluted by a landfill (see Section II.E) (Shackelford and Keith, 1976; Alford, 1975).

No quantitative information was available concerning the amounts of waste dibromopropanol disposed on land or in aqueous effluents. The aqueous wastes probably originate from water used in product purification and for washing kettles and other equipment, and land-disposed wastes came from heavy ends which were landfilled rather than incinerated. There was no information on incineration as an alternate route for dibromopropanol disposal. Since it is a fire-retardant, incineration would require additional fuel to support combustion.

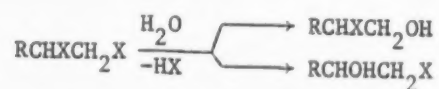
f. Other Haloalcohols

Very little information was available concerning the waste disposal of the other haloalcohols. The only data found was the reported identification of 2,2,2-trichloroethanol in industrial waste water (Shackelford and Keith, 1976). As discussed for other haloalcohols, the wastes could include washings from product purification or production equipment clean-up. Organic wastes, which are expected from haloalcohol purification, potentially contain residues and will probably be disposed by landfill.

6. Potential Inadvertent Production In Industrial Processes

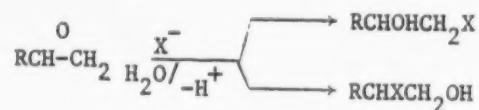
Although there was no information available on inadvertent production of the haloalcohols during industrial processes, some pathways could be suggested based upon known chemical reactions (March, 1968).

Hydrolysis reactions of vicinal dihalides could yield haloalcohols:



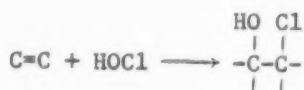
Substitution of a hydroxide group for a halide ion at the primary carbon is more likely than at the secondary position for steric reasons. Substitution at the secondary carbon would only become important if hydrolysis would proceed by a carbonium ion mechanism, and this is considered unlikely for most industrial uses of the halogenated hydrocarbons.

Reactions of epoxides with halide ions can yield haloalcohols:



This reaction represents the reverse reaction of the final stage of epoxide production by the commercial chlorohydrination process (see Section II.A.3). So any process in which the epoxides (ethylene oxide or propylene oxide) or epichlorohydrin are exposed to an inorganic halide could yield haloalcohols. Haloalcohol production by this process results from disinfection and fumigation with epoxides; this is discussed further in Section II.C.7. Some uses of epoxides, in which reactions are catalyzed by Lewis acids, yield haloalcohols as by-products. It has been observed that ethylene oxide reacts with fluoride from BF_3 to yield 2-fluoroethanol (Bedford et al., 1977). Also, any release to the environment of epichlorohydrin could be followed by hydrolysis to a haloalcohol.

The reaction of olefins with hypohalous acid (HOX) will yield haloalcohols; in fact, haloalcohols are commonly prepared in this manner (see Section II.A.3). This reaction could also be important where industrial waste water is treated by chlorination before discharge (Gould, 1959; Morris, 1975):



7. Potential Inadvertent Production in the Environment

Haloalcohols are produced in the environment by chemical or metabolic pathways. Ethylene oxide and propylene oxide are converted to haloalcohols in the environment by apparent metabolic pathways. Both epoxides are applied to stored and packaged foods as fumigants for insect control and for sterilization of microbes. In 1975 about 0.1 million lbs of ethylene oxide and smaller amounts of propylene oxide were consumed domestically as fumigants (Landels, 1976). Wesley et al. (1965) showed that the chlorohydrins (2-chloroethanol, chloropropanols) were formed by the reaction of residues of ethylene or propylene oxide with water and natural chlorides present in fumigated commodities. Heuser and Scudamore (1967) determined that 2-bromoethanol can be formed in wheat and wheat flour during fumigation with ethylene oxide. The bromine was derived either from naturally occurring inorganic bromide or from bromide produced during prior fumigation with methyl bromide. The concentrations of the chloroalcohols or bromoalcohols which may be formed is dependent upon a number of variables and can, therefore, vary widely. Concentrations of 2-chloroethanol up to 1,000 ppm were found in whole spices and ground spice mixtures after commercial fumigation with ethylene oxide (Wesley et al., 1965); however, concentrations usually detected appear to be one or two orders of magnitude lower. Because the formation of the chloro- or bromoalcohols is thought to occur from residual ethylene or propylene oxide, the amount of these halohydrins annually formed from fumigation should total only a fraction of the approximate 0.1 million lbs of oxides used.

Ethylene oxide is also used for sterilizing manufactured goods, including surgical equipment, and it can subsequently degrade to chloroethanol (Weinberger, 1971). No information on the amount of epoxide consumed in these applications is available.

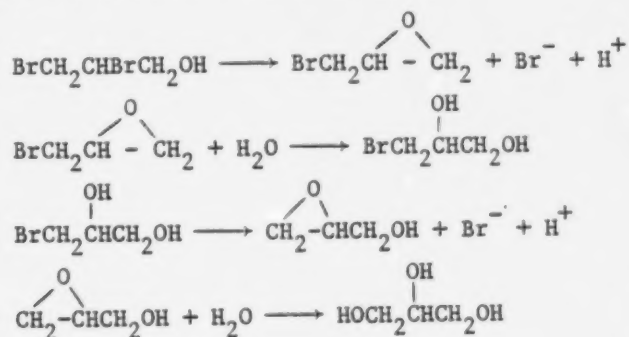
D. Environmental Pathways and Fate Effects

1. Persistence

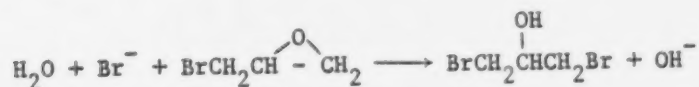
a. Biological Degradation Organisms and Products

Studies on the enzyme-catalyzed hydrolysis of 2,3-dibromo-1-propanol suggest that all chloroalcohols and bromoalcohols degrade in the environment (Castro and Bartnicki, 1968; Bartnicki and Castro, 1969). These were the only available studies on biological degradation. No information on fluoroalcohols was available. Castro and Bartnicki (1968; Bartnicki and Castro, 1969) examined the products and qualitative rates of product formation from dibromopropanol hydrolysis with enzyme extracts of a gram-negative flavobacterium which was grown from an alfalfa field soil in an aqueous broth containing $5 \times 10^{-3} \text{ M}$ dibromopropanol. The enzyme was extracted from the cells by a combination of centrifugation and sonication. The enzyme activity in the extracted solution was equivalent to activity of the bacterium cell suspension. The crude enzyme extract was partially purified, precipitated, and part of the protein fraction was placed onto Sephadex G-200. Dibromopropanol, the epihalohydrins, and epihalohydrin hydrolysis products were metabolized with the crude enzyme extract and the partially purified enzyme at pH 7. If the enzyme solution was boiled, its hydrolysis activity was lost. The earlier study (Castro and Bartnicki, 1968) demonstrated that 2,3-dibromo-1-propanol is initially converted to epibromohydrin. The subsequent reaction depends, in part, upon the added salt (KCl or KBr). Table 10 summarizes products and rates

for reactions of the epihalohydrins and their degradation products; these data were derived from incubation of 10^{-3} M substrate in 10 ml of a 0.01 M phosphate buffer (pH 7.0) and 0.25 mg of protein thermostated at 24°C . The hydrolysis of 2,3-dibromo-1-propanol followed the reaction sequence:



Bromide ion can open the epoxide to yield 1,3-dibromo-
propanol:



Incubation with the addition of 0.1 M KCl established the following equilibrium:

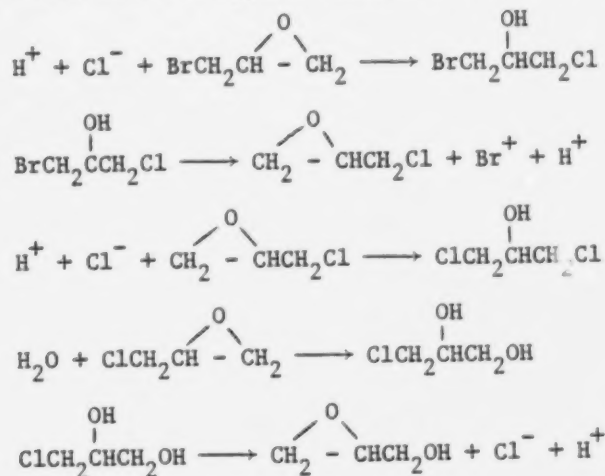


Table 10. Products from Enzymatic Conversion of Epihalohydrins and Haloalcohols
(Bartnicki and Castro, 1969)

Substrate	Added Salt (0.1 M)	Time (min)	% Conversion	Products (% yield) ^a
Epibromohydrin	KCl	1	7.4	1-Bromo-3-chloro-2-hydroxypropane ^b
	KCl	60	100	1,3-Dichloro-2-hydroxypropane, 1-chloro-2,3-dihydroxypropane, 1-bromo-2,3-dihydroxypropane
	KBr	1	2.0	1,3-Dibromo-2-hydroxypropane
	KBr	60	95	1-Bromo-2,3-dihydroxypropane, glycidol (trace)
	None	1	1.7	1-Bromo-2,3-dihydroxypropane
	None	60	81	1-Bromo-2,3-dihydroxypropane, glycidol (trace)
Epichlorohydrin	KCl	1	1.6	1,3-Dichloro-2-hydroxypropane
	KCl	60	100	1,3-Dichloro-2-hydroxypropane, 1-chloro-2,3-dihydroxypropane
	KBr	1	1.2	1-Bromo-3-chloro-2-hydroxypropane
	KBr	60	60	1-Chloro-2,3-dihydroxypropane, 1-bromo-2,3-dihydroxypropane, epibromohydrin
	None	1	0.4	1-Chloro-2,3-dihydroxypropane
	None	60	31	1-Chloro-2,3-dihydroxypropane
1-Bromo-3-chloro-2-hydroxypropane	None	5	30	Epichlorohydrin (85), epibromohydrin (15)
	None	120	100	1-Chloro-2,3-dihydroxypropane (86), 1-bromo-2,3-dihydroxypropane (14)
1-3-Dibromo-2-hydroxypropane	None	1	10	Epibromohydrin
1,3-Dichloro-2-hydroxypropane	None	10	50	Epichlorohydrin
	None	30	69	1-Chloro-2,3-dihydroxypropane, epichlorohydrin

^a Where yields are not given, products are listed in a decreasing order of significance. Yield = (moles of product/moles of substrate converted) 100.

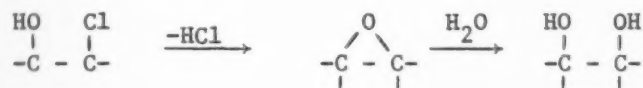
^b Yields of all single products are 100%.

Monitoring information (see Section II.E) supports a rapid degradation rate for dibromopropanol. Alford (1975) reported that dibromopropanol at a landfill test well had a concentration of 23.8 mg/l, but none was detected in leachate drawn from test wells sited outside the landfill.

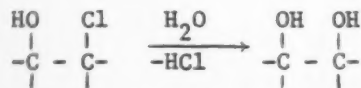
In summary, the bromoalcohols and the chloroalcohols appear to be susceptible to metabolic hydrolysis in soils. Products vary as the result of the ionic content of the media and the metabolic transformations parallel chemical reactions (see Section I.B).

b. Chemical Degradation in the Environment

The haloalcohols should chemically hydrolyze in soil and in natural water. However, their absolute hydrolysis rates, though not quantitatively known, are apparently too slow to compete with the enzyme catalyzed hydrolysis, except at high pH (10 or above). Multiple hydrolysis mechanisms could operate. Hydrolysis could proceed by pathways analogous to that described for the enzyme catalyzed hydrolysis in natural waters:

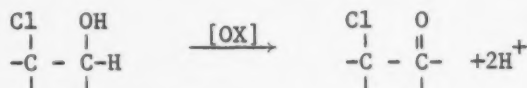


The initial product is the epoxide, which subsequently hydrolyzes to glycol. Chemical hydrolysis varies with pH. Alkaline hydrolysis follows a pathway similar to the above. At neutral or mildly acidic pH the haloalcohols directly hydrolyze:



A carbonate-catalyzed pathway could yield glycol through a cyclic intermediate (see Section I.B.1).

Environmental oxidation should not be important in water or in soil but could be a significant reaction in potable water or waste water treated by chlorination or a similar chemical oxidant (Morris, 1975). The expected product is the corresponding haloketone, haloaldehyde, or haloacid:



No rate data was available for oxidation with chlorine under water treatment conditions.

The haloalcohols are expected to degrade in the atmosphere through the free-radical reactions of the photochemical smog cycle. No direct photochemical reactivity is expected. Neither the oxidation rates nor the products from the free-radical degradation can be estimated from the information available.

2. Environmental Transport

No specific information was available on environmental transport for any haloalcohols. The physical properties (see Section I.A.1, Table 2) permit some speculation on the transport characteristics.

All haloalcohols are characterized as water soluble. They ranged from 52 g/l (25°C) for 2,3-dibromo-1-propanol to "miscible" for several haloalcohols, including 2-chloroethanol and 3-chloro-1,2-propanediol. So, they are expected to be transported as a solution in water. And, unless strong chemical or physical bonding occurs, they are expected to leach from soil.

Interphase transfer of compounds of low solubility from water to air can be estimated from water solubility and vapor pressure data (Dilling, 1977; MacKay and Leinonen, 1975). Some estimation of interphase transfer is possible, but calculated transfer rates are precluded by high solubility of

the haloalcohols. From the high solubility and the low vapor pressure (0.02 torr at 20°C) of 3-chloropropane-1,2-diol it is estimated that virtually no volatilization will occur. Other haloalcohols have vapor pressures apparently in the range 5 to 60 torr at ambient temperature, so some volatilization is expected.

3. Bioaccumulation and Biomagnification

The high haloalcohol solubilities in water indicate that they will probably not bioaccumulate or biomagnify. Neely et al. (1974) suggested calculation of a bioconcentration factor (BF) as an index:

$$\log BF = 0.542 \log K + 0.124$$

where K is the n-octanol:water partition coefficient. The high water solubilities (0.24 moles/liter) of haloalcohols lead to very low BF values, 5 or less, (K values were estimated by extrapolation, Freed et al., 1977).

E. Detection in Environmental and Biological Samples

1. Analytical Methods

Haloalcohols have been qualitatively and quantitatively analyzed by several approaches including chromatographic methods, wet chemical methods based upon halide ion analysis, and spectrometric methods. Chromatography, especially gas chromatography (GC), appears the best quantitative analytical approach with respect to selectivity and detection limit.

GC has apparently replaced older, alternative forms of chromatography such as paper chromatography and thin layer chromatography for haloalcohol analysis. GC has been applied to the analyses of haloalcohols in food (Fishbein, 1972), air (Taylor, 1977), and water (Alford, 1975). Information on GC detection methods, analytical columns, and sample collection and pretreatment will be presented in detail.

The most common GC procedures utilize stainless steel or glass columns packed with Carbowax M on Chromosorb W (Fishbein and Zielinski, 1967; Ragelis et al., 1966, 1968; Brobst and Tai, 1971; Webb et al., 1973; Garrett and Lambert, 1966); the carbowax M content varied from 4% to 20%. Operating temperatures of 65°C to 115°C were used. Other columns include 10% FFAP on Chromosorb W (Taylor, 1977), Poropak Q (Pagington, 1968), silicone oil on Diatoports, polyethylene glycol on celite (Fishbein, 1972), OV-17 on Gas-Chrom Q (Humbert and Fernandez, 1976; Breimer et al., 1974); SE-30 on Chromosorb G or W (Herbolsheimer and Funk, 1974; Vesterberg et al., 1975), and SF-1150 on Chromosorb W (Anderson et al., 1966).

Several detection systems have either been applied to haloalcohols or to analogous halogenated alkanes. Flame-ionization detection (FID) has been perhaps the most common GC detector used. It has been generally recommended for haloalcohol analysis in foods (Ragelis et al., 1966, 1968; Brobst and Tai, 1971) and for air analysis (Taylor, 1977). The absolute detection limit is on the order of 10 ng. The limits of detection for food analysis (which includes sample collection and treatment, as well as the detector response is consistently in the ppm (mg haloalcohol/kg sample) range for ethylene and propylene chlorohydrin and bromohydrin detection. The NIOSH Manual of Analytical Methods (Taylor, 1977) suggests the flame-ionization detector for 2-chloroethanol (ethylene chlorohydrin) analysis in air. The flame-ionization detector is non-selective, so interferences could become a problem.

The thermal conductivity detector has a detection limit in the μg range. Like the flame-ionization detector, the thermal conductivity detector is non-selective.

Electron capture detection (ECD) is more selective than flame-ionization or thermal detection, since haloalcohol measurement is based upon halogen content. It will respond to other halogenated hydrocarbons, and other organics with low ionization potentials such as polyaromatics, and substrates with other functional groups containing heteroatoms (Zweig, 1970). The detection limit depends upon the number of halogen substituents; limits are below the nanogram range. ECD has been applied to haloalcohol analysis (Fishbein, 1972) and haloalcohols (e.g., trichloroethanol) have been used for preparing chlorinated esters to increase the ECD detection limits of organic acids (Smith and Tsai, 1971). A disadvantage of ECD is that it does not have a linear response.

Microcoulometric detection is a highly selective and sensitive system for halogenated organic substrates. It operates by degrading the organic compound (oxidation or reduction procedures can be employed) and subsequently measuring the liberated halide. It has a good linear response range and is capable of measuring halogenated hydrocarbons in the nanogram range (Hall, 1974). No information on its application to haloalcohol analysis was available.

Pagington (1968) described use of a ozatron type J detector element from A.E.I. leak detector type HA for chlorohydrin analysis. A detection level of 0.2 ppm was reported for injection of 25 μl samples.

Mass spectral detection (MS) is the most selective method for identification of an organic substrate and also has potential for detection at the nanogram range. Alford (1975) has reported the application of GC-MS for identifying 2,3-dibromo-1-propanol in environmental samples. The method used for this identification was the general approach of Webb and co-workers (1973).

Sample preparation appears to be a critical stage of any analytical procedure. The haloalcohols are chemically reactive and could eliminate HCl to yield the epoxides, bond with hydroxylated materials, or participate in other reactions. Pfeilsticker and co-workers (1974) also noted that samples containing ethylene oxide (such as would be expected from a plant manufacturing or using the epoxide) can react with chlorides (e.g., NaCl or CaCl_2) added during work-up, thus yielding 2-chloroethanol.

Haloalcohol (2-chloroethanol and the chloropropanols) analysis in foodstuffs is complicated by its bonding to hydroxyl groups in starch. The halohydrins cannot be quantitatively recovered by simple ether extraction. Brobst and Tai (1971) employed an acid hydrolysis treatment with 2 N H_2SO_4 in a pressure bottle. The hydrosylate was then extracted with ether and the extract was concentrated on a Kuderna-Danish system. They claimed recovery of 90% for 5 ppm of the propylene chlorohydrins (chloropropanols).

Whitbourne and co-workers (1969) evaluated recovery of chloroethanol from plastic and rubber utilized in surgical equipment. Their procedure was to heat samples in conventional round-bottom flask (ground-glass joints) at 80°C to 90°C under vacuum (20 μ) and collect all distilled material in a cold U-tube (liquid nitrogen). Chloroethanol recovery was excellent from PVC plastic (100%), somewhat lower for latex rubber (ca. 87%), and poor in synthetic rubber (38.0%).

Weinberger (1971) described a co-sweep distillation process for sampling ethylene chlorohydrin in manufactured goods, including natural and

synthetic fiber. Preweighed samples were heated (110°C) with water. Carrier gas (nitrogen) was swept through the system. Isooctane, which was intermittently injected into the system, was trapped along with chloroethanol in Teflon cooling coils. The isooctane solution was subsequently analyzed by GC. Weinberger reported about 90% to 102% recovery for 1.5 to 48.0 µg of chloroethanol added to 1.0 to 1.6g of sample.

Several groups have evaluated GC for analysis of trichloroethanol in blood and in urine. It is an important analysis, since trichloroethanol is a metabolite of trichloroethylene and is a sedative. Until GC became the preferred analytical method, trichloroethanol was examined by a colorimetric method (see below). It is present in blood and in urine as free alcohol and bound with D-glucuronide. Methods have been published for analysis of both free alcohol and total alcohol. The latter analysis requires hydrolysis of glucuronide.

Two methods of hydrolysis of bound trichloroethanol have been reported. An enzymatic hydrolysis utilizes β -glucuronidase (Garrett and Lambert, 1966; Ogata and Saeki, 1974), which can be obtained from liver extracts. Concentrated sulfuric acid has also been used to hydrolyze the trichloroethyl glucuronide (Humbert and Fernandez, 1976; Breimer et al., 1974; Vesterberg et al., 1975; Ogata and Saeki, 1974; Herbolzheimer and Funk, 1974). The trichloroethanol can be subsequently taken for sampling either by extraction (Garrett and Lambert, 1966; Ogata and Saeki, 1974; Humbert and Fernandez, 1976) or head-space sampling (Breimer et al., 1974; Triebig et al., 1976). No study has systematically attempted to compare combinations of these treatments. Both methods, when utilized with GC-ECD, have detection limits in the µg/ml range or below.

Anderson et al. (1966) evaluated recovery of 0.1 ppm trichloroethanol added to animal tissue and crops (wet and dry). Their method homogenized the sample plus 0.1 N H_2SO_4 , then extracted organic substrates with ethyl ether and analyzed them by GC-ECD. Trichloroethanol recovery ranged from 44% to 68% in dry crops, from 61% to 68% in animal tissues, and from 51% to 92% in moist crops.

No specific procedure for sample treatment was available for haloalcohol analysis in water. The general procedure described by Webb and co-workers (1973) was used in a study which identified 2,3-dibromo-1-propanol in a water sample and it appears generally applicable. It consists of extracting the water (applicable solvents include chloroform, petroleum ether, hexane, and ethyl ether); the haloalcohols will be present in the neutral (pH 5-7.5) range. The solution is then concentrated by Kuderna-Danish system. No information on haloalcohol analytical recovery from water was available.

For atmospheric analysis NIOSH (Taylor, 1977) has developed a standard procedure for 2-chloroethanol (ethylene chlorohydrin) using commercially available two-section activated charcoal tubes. These contain 150 mg of coconut shell charcoal split by a polyurethane plug into sections of 100 mg (front) and 50 mg (rear). The rear section was designed to test if the sample broke through the front section. The NIOSH method was tested by sampling 20 l of air at a rate of 0.2 l/min. The chloroethanol was desorbed with 5% isopropyl alcohol in carbon disulfide and then measured by GC-FID analysis. The coefficient of variation for the overall sampling and analysis was 0.076 for 2-chloroethanol concentrations of 7 to 30 mg/m^3 . At 5 ppm (16 mg/m^3) the standard deviation was $\pm 1.22 mg/m^3$. Analytical recovery was 5.8% greater than the "true" value when 5 ppm was analyzed.

Baker and co-workers (1971) evaluated photoelectron spectrometry (PES) as an alternative method to GC for quantitative analysis of haloalcohol residues in food as the result of fumigation with propylene oxide and with ethylene oxide. They stated that the method was feasible, since PES of the individual haloalcohol residues could be distinguished, but no detection limits were reported.

The Fujiwara reaction has been used for screening trichloro-compounds, including trichloroethanol, in urine. (Moss and Kenyon, 1964; Tanaka and Ikeda, 1968; Ogata et al., 1970). The method requires oxidation of the trichloroethanol to trichloroacetic acid and then reaction of the acid with pyridine. The analysis consists of colorimetric measurement of the reaction product at 530 nm. The method is not specific for trichloroethanol but is a general approach for trichloro-compounds. The method is now dated and gas chromatographic analysis has replaced it (see above).

Dolmatova-Guseva and Aizenshadt (1971) described a wet chemical analytical method for atmospheric 2-chloroethanol. The haloalcohol was trapped in a sparging tube with water as solvent. It was hydrolyzed to ethylene glycol, which was then quantitatively measured by colorimetric assay of its phenylhydrazone. Analytical recovery and detection limits were not available.

Kheifets and co-workers (1969) described a polarographic procedure for measuring mixtures of 3-chloro-1,2-propanediol and 2,3-dichloro-1-propanol. The method first required converting these chloroalcohols to the corresponding iodoalcohols by refluxing with KI in glycerol. With differential analysis the authors reported analysis of samples containing 3%-5% of 2,3-dichloro-1-propanol.

Haloalcohols can be quantitatively analyzed by combustion to liberate halide (Sokolov, 1964). The resulting halide can be measured by a variety of titrimetric methods, specific ion electrode, or other analysis. The method can detect low concentrations (1 μ g or less as halide) but has virtually no selectivity.

2. Monitoring

Available monitoring data has indicated the presence of haloalcohol only in industrial waste water and near industrial waste land disposal sites. Although no haloalcohol detection has been reported in ambient samples or in the atmosphere nearby industrial sites, few monitoring studies definitively attempted to identify haloalcohols.

Pervier and co-workers (1974) and Gruber (1976) described environmental discharge of two haloalcohols (dichloropropanol and 3-chloro-1,2-propanediol) from epichlorohydrin and glycerol (via epichlorohydrin hydrolysis) production plants. Their description was derived from information submitted by manufacturers, but the report had no specific information on how the manufacturers generated the data. According to both reports, haloalcohols are not emitted to the atmosphere. If it is safe to assume that the information was derived, at least in part, from monitoring by the manufacturer and that the manufacturers specifically sought haloalcohols, then it appears that insignificant quantities are emitted. Both Pervier et al. and Gruber have noted that land disposed wastes contain dichloropropanols. Gruber also reports dichloropropanol in wastewater effluent.

Shackelford and Keith (1976) have collected and summarized monitoring data for organic chemicals. The haloalcohol identifications which

they indexed are summarized in Table 11. All haloalcohol observations were associated with industrial waste disposal; these include their identification in waste-water discharge and landfill leachate. The dichloropropanol observation at sea refers to its observation in a group of barrels of industrial waste dumped at sea (Greve, 1971).

Alford (1975) was the source of the Shackelford and Keith citation of 2,3-dibromo-1-propanol in well water. The referenced wells were built to monitor and recover leachate that was entering a ground water supply from a Newcastle, Delaware landfill (Table 11). A dibromopropanol concentration of 23.8 mg/l was measured at a well drilled at the landfill; it was the organic pollutant present in the highest concentration. However, no dibromopropanol was detected at recovery wells sited below the landfill.

Antipina (1957) reported that the concentration of 2-chloroethanol was 0.01-0.45 g/l in waste water at an ethylene oxide manufacturing plant. The citation apparently referred to the waste water before its treatment. The effluent composition was not available in this citation.

Table 11. Monitoring Information on Haloalcohols in Water
(Shackleford and Keith, 1976)

<u>Haloalcohol</u>	<u>City or Reference</u>	<u>Source</u>
2-Chloroethanol	Calvert City, KY	Effluent (Chem)
	Calvert City, KY	Effluent (Latex)
	Pacolet and Enoree River	Effluent (Chem)
Trichloroethanol	Calvert City, KY	Effluent (Chem)
	Calvert City, KY	Effluent (Latex)
2,3-Dibromo-1-propanol	Dover, DE	Landfill leachate
	Dover, DE	Landfill leachate
	Alford, 1975	Well
	Newcastle County, DE	Effluent (Landfill leachate)
	WHO Tech. Report 7	Effluent (Acryl)
1,3-Dichloro-2-propanol	Louisville, KY	Effluent (Chem)
	Louisville, KY	Effluent (Chem)
Dichloropropanol	Greve (1971)	Sea

III. Health and Environmental Effects

A. Humans

1. Occupational Exposure and Poisoning Incidents

Fluoroethanol, in common with other alkyl fluorocarbons of even numbered chain length, is a potent mammalian poison (Chenoweth, 1949). By lethal synthesis of fluorocitrate these halocarbons prevent dehydration of citric acid by aconitase and produce a blockade of the Krebs cycle (Peters, 1952).

Numerous cases of accidental poisoning have been reported (Chenoweth, 1949) with initial symptoms of nausea, apprehension and subsequent epileptiform convulsions. Exposure to high concentrations of fluoroethanol leads to loss of consciousness and ventricular fibrillation. A case of a two-year old boy who licked a rodenticide bottle was cited by Moeschlin (1965). After a six hour delay, vomiting, irregular breathing, tetanic convulsions, and coma developed. Improvement was not seen until after approximately four days. The incidence of cardiac or central nervous system symptoms may relate to diet (Saunders, 1957) since carnivores seem to develop more incidences of fibrillation than do herbivores. Three cases of industrial poisoning by fluoroethanol vapor were examined by Colamussi et al. (1970). Initial symptoms included nausea, headache, and tremors. Vertigo and asthenia were noted in two cases. One worker had slight hypoglycemia and another had signs of a moderately enlarged liver. Since these were accidental situations, no concentration estimates could be deduced.

Industrial exposure to chloroethanol at high concentrations has resulted in several fatalities. Two cases were described in an early report by Koelsch (1927). A paper factory worker cleaning a metal cylinder with cloth dipped in chloroethanol developed nausea, headache, vomiting, and stupor

continuing through death. Autopsy revealed hyperemia of the liver and lungs. In the second case a linoleum factory worker developed early morning symptoms of drowsiness and slight vomiting followed by recovery. Later that evening he developed fatal breathing difficulties. Edema of the lungs and brain was shown at autopsy. Dierker and Brown (1944) described a worker exposed to 305 ppm vapor and cutaneous absorption who expired. Kidney congestion was noted at autopsy.

Goldblatt and Chiesman (1944) described a fatality involving a worker exposed to a high concentration of hot chloroethanol vapor for 90 minutes. Death occurred in 14 hours, and slight cerebral edema was noted post mortem. Another worker (Goldblatt and Chiesman, 1944) exposed to chloroethanol vapor over a two month period showed symptoms of headache, confusion, and hematuria. Autopsy revealed renal necrosis, especially in the convoluted tubules, and gross edema of the basal ganglia. Ballotta et al. (1953) reported a fatality resulting from oral ingestion of a small quantity of chloroethanol. Nausea and headache were followed by excitement and coma. Hyperemia of the brain, liver, and kidneys were shown by pathology. Several deaths of agricultural workers who used chloroethanol to accelerate potato sprouting have been reported (Bush et al., 1949). Vomiting, nausea, weakness, and respiratory failure were symptoms described. Saitanov and Kononova (1976) reported a poisoning incident with chloroethanol in a 24 year-old subject. Central nervous system effects led to depressed respiration and cardiovascular activity, collapse, and ensuing hypoxia. Kidney and liver function were disturbed and protein, electrolyte and serum enzyme changes were noted. Irreversible damage to the heart, kidneys and liver was reported, but the role of systemic hypoxia could not be evaluated as a contributing cause in this damage.

Trichloroethanol exposures have not been described in man. However, since metabolism of both trichloroethylene and chloral hydrate in human subjects has been shown to produce rapid blood levels of trichloroethanol, and this alcohol in itself has equipotent hypnotic effects (Imboden and Lasagna, 1956), any reported human toxicity for chloral hydrate and trichloroethylene should be considered relevant. Chloral hydrate is irritating to the skin, induces nausea, vomiting and gastric distress. Ingestion of 5 grams or less of chloral hydrate has produced fatalities. Central nervous system effects include respiratory depression and hypotension. At high levels of exposure, renal irritation, liver damage, and depressed myocardial contractility have been shown. Chronic use in addicts has resulted in dermatitis, gastritis, and parenchymatous renal damage. Bauer and Rabens (1974) investigated trichloroethylene toxicity resulting from occupational exposure in four male workers using this compound for cleaning or degreasing. Resulting dermatitis included exfoliative, papulovesicular forms and erythroderma. Other symptoms included mucous membrane irritation of the eyes and upper respiratory tract, inebriation, and one case of toxic hepatitis. Trichloroacetic acid was found in the urine, and trichloroethanol in the serum, of these workers.

Acute trichloroethylene exposure in industrial accident situations has elicited symptoms of nausea, vomiting, mental agitation, abdominal cramps, and lower back pains (Waters et al., 1977). Death resulting from accidental ingestion of a large quantity of trichloroethylene in one worker revealed, on autopsy, liver necrosis as well as pancreatitis and nephrosis (Kleinfeld and Tabershaw, 1954). The "psycho-organic syndrome" developed during long term exposure to trichloroethylene has been described repeatedly (Waters et al., 1977); symptoms include unrest, sleeplessness, fatigue,

disturbed vision, vomiting, burning of the eyes, and intolerance to alcohol. In general, these symptoms disappeared when the subject was removed from the source of exposure. Exposure to 100 ppm trichloroethylene for 4-6 hours can produce blood levels of ~3 mg/l trichloroethanol with accompanying CNS effects (Guberan, 1977). In a study of seventy workers exposed chronically to trichloroethylene, Gravoac-Leposavic et al. (1964) reported dysproteinemia, decreased serum albumin levels, positive thymol turbidity tests, and positive cephalin-cholesterol tests, thus indicating some impaired hepatic function.

No direct human exposure data for trifluoroethanol has been found. In animal studies, trifluoroethanol is the most toxic urinary metabolite identified after halothane anesthesia (Airaksinen, 1970). Both halothane and fluroxene anesthesia result in exposure to trifluoroethanol, but human metabolism produces less of this toxic metabolite than other species (rodents, dogs). Phenobarbital pretreatment of monkeys increases the ratio of trifluoroethanol to trifluoroacetic acid produced from fluroxene and correspondingly increases toxicity (Fiserova-Bergerova, 1977); this interaction should be considered relative to human exposures. Human toxicity data relating to fluorothane and fluroxene should also be reviewed in evaluating trifluoroethanol. Halothane was implicated in human liver damage in a number of cases (Lindenbaum and Leifer, 1963). In a major review, Little (1968) found that over a ten-year period (1957-1967) there were 404 reported cases of halothane related liver injury, of which 144 were fatal. A significantly higher incidence of death was found if this population was screened for patients having received halothane anesthesia more than once. Symptoms of halothane-induced injury reported were fever, anorexia, nausea, and vomiting. Autopsy revealed hepatocellular necrosis, mainly in the centrolobular region. Fluroxene toxicity

after anesthesia has been reported (Harris and Cromwell, 1972; Reynolds et al., 1972; Wollman and Surks, 1973; Tucker, 1973), with hepatic damage as the major toxic effect.

Since all of the haloalcohols have potential for toxicity to the liver, and since human metabolism of these alcohols takes place at this site as well, this interrelationship should be kept in mind when evaluating biological half-life and bioaccumulation of these compounds. The evidence from evaluation of patients who have experienced multiple halothane anesthesia (Little, 1968) is suggestive. Work by Ertle et al. (1972) on trichloroethanol blood levels in volunteers, indicates that the alcohol accumulates over successive days' exposure to trichloroethylene. If elimination and biotransformation would become impeded, toxic potential would thereby increase.

2. Epidemiology Studies

No epidemiological studies on the haloalcohols have been reported.

3. Controlled Human Studies

Controlled human studies involving the haloalcohols have not been conducted.

B. Reported Effects on Nonhuman Animals from Industrial Release, Spills, and Accidents

No data concerning accidental exposures to animals from industrial sources, spills, or accidents are available.

C. Experimental Studies on Nonhuman Animals

1. Toxicity and Effects on Mammals

a. Absorption, Transport, Tissue Distribution, Metabolism, and Excretion

3-Chloro-1,2,-propanediol

Jones et al. (1969) observed that Wistar rats dosed orally or intraperitoneally with 3-chloro-1,2-propanediol (50 mg/kg) excreted the urinary metabolites 2,3-dihydroxypropyl-5-cysteine and its N-acetate, as well

as the unchanged compound. Further studies by Jones (1975) indicated that the 3-chloro, 3-bromo, and 3-iodo propanediols were detoxified by conjugation with glutathione. Twenty to thirty percent of 3-chloro-1,2-propanediol is excreted as CO_2 , and 10% is found unchanged in the urine. The postulated pathway for metabolism (Figure 7) is conversion first to the epoxide, glycidol (VI), via dehalogenation, and subsequent hydrolysis of the epoxide to glycerol. The epoxide could be formed enzymatically (Castro and Bartinicki, 1968)

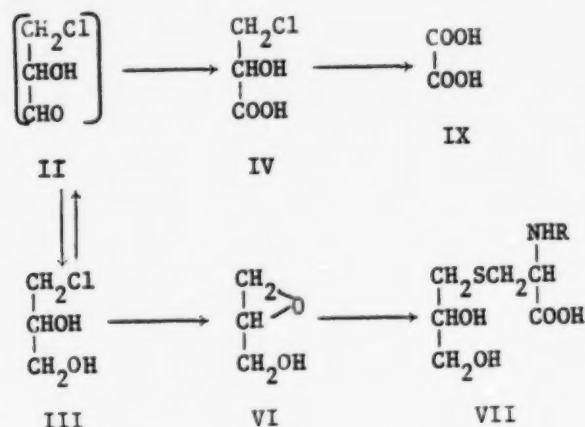


Figure 7. The metabolism of 3-chloro-1,2,-propanediol (III) and this more reactive species (~50 times) would interact with glutathione either directly or via the enzymatic activity of glutathione-S-epoxide transferase (Boyland and Williams, 1965). Jones (1975) has shown that epoxide formation occurs readily in vitro at pH 8. However, attempts to produce glutathione alkylation in vitro with the propanediols and a rat liver enzyme preparation did not succeed. Glycidol (VI) in the presence of rat liver enzymes did produce 50% to 60% alkylated glutathione in vitro over a three hour incubation period. Edwards et al. (1975) found labelling of the lipid fractions

of brain, testis, caput epididymis, and cauda epididymis after intravenous injection of (^{14}C) 3-chloro-1,2-propanediol (uniform label). Jones et al. (1977) discusses 3-chloro-1,2-propanediol oxidation (see Figure 7) to chlorolactic acid (IV) through a postulated aldehyde (II) by the action of a NAD linked dehydrogenase.

Crabo and Appelgren (1972) carried out whole body autoradiographs in albino mice and rats that were given an intravenous injection of radioactive (^{14}C) 3-chloro-1,2-propanediol (position of label not specified). The rat specimens showed a high concentration of drug in the cauda epididymis, unlike comparable sections from the mouse. Both species showed high concentrations of radioactivity in liver, bile, kidney, and urinary bladder shortly after injection (60 minutes).

2,2,2-Trichloroethanol

Trichloroethylene inhalation in man produces the major metabolites trichloroethanol, trichloroacetic acid, and trichloroethanol glucuronide (Figure 8). The biological half-life of trichloroethanol in the blood of

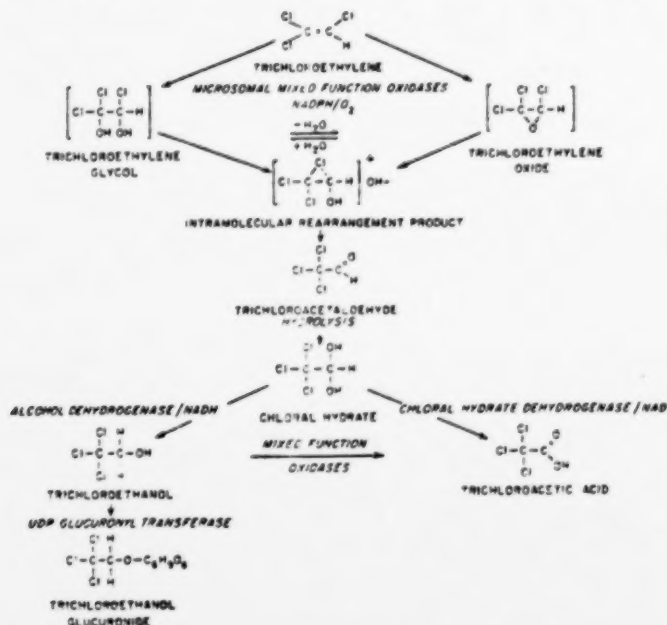


Figure 8. Proposed intermediary metabolism of TCE (Waters et al., 1977).

volunteers exposed to 50 or 100 ppm trichloroethylene is ~12 hours (Ertle et al., 1972). Müller et al. (1974) determined a biological half life (plasma) of ~13 hours in humans given 10 mg/kg oral trichloroethanol. Glucuronidation occurs in the liver, and excretion of the trichloroethanol glucuronide by the kidneys is rapid. A major increase in the urinary half-life of trichloroethanol has been reported in a patient addicted to trichloroethylene (Ikeda, 1977). Plasma half-life values for trichloroethanol vary with species; Clifford (1977) reported values of 10 hours in the Rhesus monkey and two hours in the squirrel monkey. Fernandez et al. (1975) in a study of human absorption of trichloroethylene (97 ppm, 8 hrs.) has shown that only ~50% of the trichloroethylene absorbed is recovered as the urinary metabolites trichloroethanol (32.7%) and trichloroacetic acid (17.7%) within 16 days after exposure; other metabolites are therefore believed to result in man. Dalbey and Bingham (1978) have shown that phenobarbital pretreatment of rats (75 mg/kg for 4 days) increased trichloroethanol formation from trichloroethylene. Administration of ethanol simultaneously with chloral hydrate increases trichloroethanol levels in vivo for mice (Gessner, 1973), dogs (Kaplan et al., 1969), and man (Kaplan et al., 1967), most probably through inhibition of trichloroacetic acid formation.

2,2,2-Trifluoroethanol

Blake et al. (1967) investigated the metabolism of radioactively labelled ($^{14}\text{CF}_3$) trifluoroethanol administered intraperitoneally to mice (Figure 9). Analysis of pooled 48-hour urine samples indicated that trifluoroethanol glucuronide and trifluoroacetate in a ratio of 6:1 could account for over 80% of the urinary radioactivity. Further studies (Blake et al., 1969) indicated that increasing the initial dose of injected radiolabelled

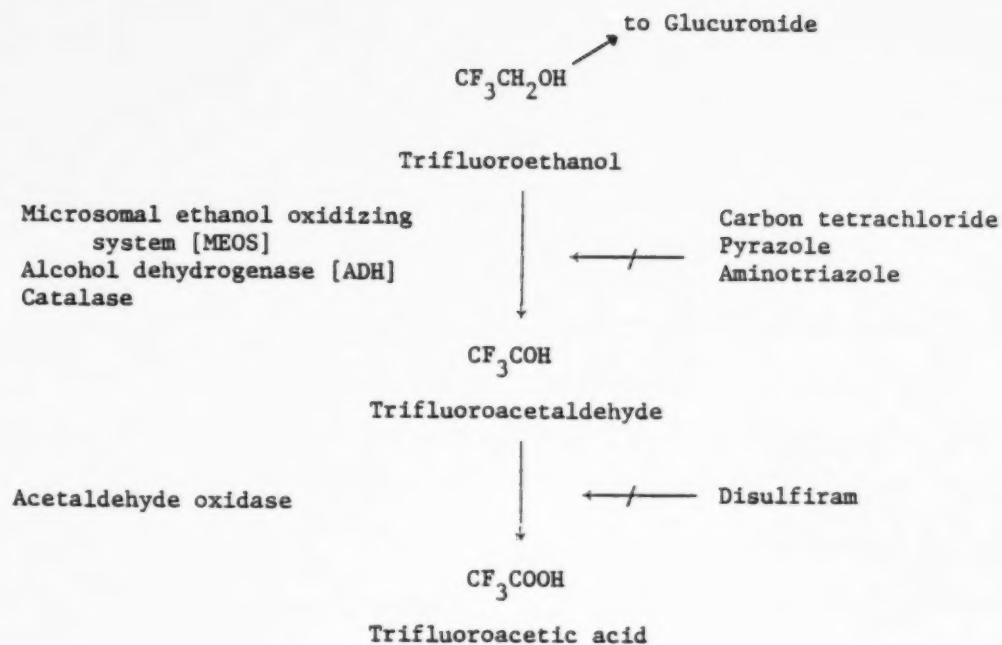


Figure 9. Metabolism of Trifluoroethanol.
(Cascorbi and Singh-Amaranth, 1973)

trifluoroethanol decreases the proportion of radioactivity appearing in the urine at 48 hours. Ethanol treatment (1200 mg/kg every four hours for 12 hours) decreased the percentage of urinary trifluoroacetate excreted after trifluoroethanol injection. Allopurinol increased the toxicity of trifluoroethanol and trifluoroacetaldehyde hydrate in mice, suggesting that inhibition of trifluoroethanol conversion to trifluoroacetate via xanthine oxidase resulted in accumulation of the more toxic metabolite trifluoroethanol (Airaksinen, 1970). Cascorbi et al. (1976) showed that trifluoroethanol toxicity was greater in male mice than in females, and that this sex difference could be reversed by treatment with the opposite sex hormones. This may be related to greater hepatic microsomal enzyme activity in males. Trifluoroethanol metabolism in two human volunteers was shown to result in urinary excretion of primarily trifluoroacetate (Cascorbi and Blake, 1971). Only 15% of injected radiolabelled trifluoroethanol could be identified as the glucuronide conjugate. However, it should be noted that the total percentage of radioactive urinary metabolites collected in six days varied markedly in the two subjects (80.5%, 53.3%). Phenobarbital pretreatment in rhesus monkeys has increased the toxicity of fluroxene (Munson et al., 1975) by the postulated mechanism of increasing the ratio of trifluoroethanol to trifluoroacetate produced by metabolism in this species. Drugs that have been shown to affect trifluoroethanol metabolism and toxicity include (besides ethanol, allopurinol, and phenobarbital) disulfuram, carbon tetrachloride, methylcholanthrene, and pyrazole (Fiserova-Bergerova, 1977).

2-Chloroethanol

The observation by Johnson (1965) that oral administration (55 mg/kg) of 2-chloroethanol reduced rat kidney and liver glutathione levels

prompted this group to investigate 2-chloroethanol metabolism in vivo. Chromatography of rat liver and kidney tissue extracts after oral administration of 2-chloroethanol (100 mg/kg) showed that S-carboxymethyl glutathione had been formed (Johnson, 1967). Reaction of 2-chloroethanol with glutathione in vitro could not produce this metabolite. Ethanol (500 mg/kg) was found to protect against the in vivo 2-chloroethanol induced glutathione depletion. Johnson showed that 2-chloroethanol is both a substrate for, and an active inhibitor of, yeast and liver alcohol dehydrogenase. Based on this evidence, a postulated metabolic pathway was proposed by which chloroethanol is converted to the -SH reactive metabolite, chloroacetaldehyde, by the action of alcohol dehydrogenase. Blair and Vallee (1966) has shown that purified human liver alcohol dehydrogenase will oxidize 2-chloroethanol at approximately 20% of the rate of ethanol (pH 9.3). Evidence from numerous in vitro mutagenicity assays confirms that the activity of 2-chloroethanol increases after activation with liver microsomal enzymes. (Section III, C., 1., f.)

No data concerning tissue distribution of 2-chloroethanol in vivo is available. However, work on vinyl chloride (VCM) distribution (Hefner et al., 1975) should be considered relevant. Monochloroacetic acid has been found as a urinary metabolite after VCM inhalation by rats, and has been found in the urine of workers exposed to VCM (Grigorescu and Toba, 1966); 2-chloroethanol is a likely intermediate in the formation of this metabolite. VCM inhalation produces decreased rat liver sulfhydryl group content, and ethanol inhibits VCM metabolism in vivo (50 ppm exposure). Hefner et al. (1975) reported that rats exposed to 50 ppm VCM for 65 minutes showed 58% of radioactive label in the urine, 2.7% in the feces, and 9.8% in expired CO₂ within 15 hours. By 70 hours, 67% of the radioactivity had been excreted

in the urine, 3.8% in the feces, and 14% as expired CO₂. Five hours later examination of tissues showed that 1.6% of the radioactivity remained in the liver, 0.2% in the kidneys, 3% in the skin, and 7.6% remained in the carcass.

b. Acute Toxicity

3-Chloro-1,2-propanediol

Acute toxicity data for 3-chloro-1,2-propanediol are summarized in Table 12. Jackson and Robinson (1976) investigated the toxicity of 3-chloro-1,2-propanediol and found that 5 of 12 male Wistar rats died after a single oral dose of 100 mg/kg. An investigation in mice indicated an LD₅₀ of 73 mg/kg for 3-chloro-1,2-propanediol by intraperitoneal injection (Hirsch and Kolwyck, 1975). Commercial 3-chloro-1,2-propanediol is an unstable racemic mixture. Jackson et al. (1977), using redistilled 3-chloro-1,2-propanediol, reported an LD₅₀ of 100 mg/kg after a single oral dose of the racemic mixture. Resolution of the mixture into its isomers and preliminary testing indicates that the R(-) (dextrorotatory) form shows lethal toxicity at 75 mg/kg in Wistar rats (oral) while the S(+) 3-chloro-1,2-propanediol is not lethal at 150 mg/kg. The 1-amino analogue is also an active antifertility agent, and shows a similar stereospecificity. Coppola and Saldarini (1974) have shown that the 1-amino analog of 3-chloro-1,2-propanediol has a differential toxicity when resolved, the l(-) form being at least 10 times less toxic since it is not lethal at 500 mg/kg in rats. The d(+) amino analog had an oral LD₅₀ of ~50 mg/kg in male rats. Dorobantu et al. (1970) injected rats of both sexes (injection route not specified) with 3-chloro-1,2-propanediol (unknown purity) and determined an LD₅₀ of 127 mg/kg. Subsequent pathology revealed extensive cortical necrosis of the kidneys. Para-aminosalicylic acid (PAS) staining casts were found in the lumina. At 7 to 21 days intense regenerative phenomena in the tubular

Table 12. Acute Toxicity of 3-Chloro-1,2-propanediol

Route	Sex	Species	Strain	LD ₅₀	Reference
Oral	M	rat	Wistar	~100 mg/kg	Jackson et al., 1977
I.p.		rat		10 mg/kg	National Academy of Sciences, 1953
Ihl.		rat		~125 ppm/240 min*	Carpenter et al., 1949
Oral		mouse		160 mg/kg	Hine et al., 1956
I.p.		mouse		73 mg/kg	Hirsch and Kolwyck, 1975
Oral	M	rat		55 mg/kg	Paul et al., 1974
S.c.		rat		127 mg/kg	Dorobantu et al., 1970

*Approximate LC₅₀.

epithelia were noted. Circulatory congestion was seen in other organs, including the brain, lungs, liver, and myocardium. Kidney damage was reflected in significantly ($p < 0.01$) reduced kidney levels of the enzymes glutamic-oxalacetic transaminase (GOT) and glutamate-pyruvate transaminase (GPT). Jones et al. (1977) has postulated that kidney damage is the result of metabolic formation of β -chlorolactic acid and oxalic acid in the rat.

2-Chloroethanol

Acute toxicity data for 2-chloroethanol are summarized in Table 13. The inhalation by rats (150 minutes) of air, which was passed through pure liquid chloroethanol, produced fatalities (Ambrose, 1950). Rats exposed for 60 minutes to air passing through aqueous 2-chloroethanol solutions of 12.5%, 25%, or 50% died one to two hours after being removed from the chamber, while those exposed for 60 minutes to air filtered through a 6.25% solution were not affected. A concentration of 7.5 ppm for one hour was reported to be fatal, while 4 ppm over the same time was not. This lethal range is lower than the value of 32 ppm reported by Carpenter et al. (1949). However, two exposures of one hour each with an interspersed two hour interval did produce fatalities at 4 ppm, indicating a cumulative effect. Lawrence et al. (1971a) placed mice in inhalation chambers with air (1 l/min) bubbled through 30% aqueous 2-chloroethanol. With 80% vapor saturation being reached in 14 minutes, mice showed 50% mortality in 13.3 minutes. In the same procedure, but with a doubled air flow rate, Lawrence et al. (1972) showed that male ICR mice had 50% mortality in three minutes exposure to the chloroethanol metabolite, chloroacetaldehyde (80% vapor saturation in 7 min).

Dermal toxicity studies of 2-chloroethanol indicate that it is very effectively absorbed through the skin. Lawrence et al. (1971a) found

Table 13. Acute Toxicity of 2-Chloroethanol

Route	Sex	Species	Strain	LD ₅₀	Reference
S.c.		neonatal rat		56 mg/kg	Balazs, 1976
I.p.	M	rat	Charles River	64 mg/kg	Lawrence et al., 1971a
I.p.	M	rat	Sprague Dawley	44 mg/kg	Peterson et al., 1968
Ihl		rat		32 ppm/240 min *	Carpenter et al., 1949
Dermal		guinea pig		285 mg/kg	Wahlberg and Boman, 1978
I.p.	F	guinea pig	Huntly	84 mg/kg	Lawrence et al., 1972
Ihl		guinea pig		918 ppm/113 min	NIOSH, 1977
Oral	M	mouse	Swiss	81.4 mg/kg	Lawrence et al., 1971a
I.p.	M	mouse	Swiss	98.3 mg/kg	Lawrence et al., 1971a
Ihl		mouse		385 mg/m ³	NIOSH, 1977
S.c.		frog		250 mg/kg	Goldblatt and Chiesman, 1944
I.p.	M,F	rabbit	New Zealand	84.6 mg/kg	Lawrence et al., 1971a
Dermal	M,F	rabbit	New Zealand	67.8 mg/kg	Lawrence et al., 1971a

*LD_{Lo}.

that 68 mg/kg of compound in cotton gauze pads applied to unabraded rabbit skin for 24 hours was an LD₅₀ concentration. No significant dermal irritation in rabbit skin was noted. However, when 2-chloroethanol was injected intradermally in undiluted form, marked irritation was produced. Solutions of 1% to 5% (v/v) gave marginal irritation. Guess (1970) noted trypan blue skin spreading and severe erythema following intracutaneous injection of 2-chloroethanol (undiluted and 1/10 aqueous dilution) in rabbits. Only a faint reaction was observed at 1/50 dilution of compound. Histologic examination revealed localized edema, cellular destruction, and infiltration with numerous polymorphonuclear leucocytes and lymphocytes. Wahlberg and Boman (1978) found that 0.1 ml 2-chloroethanol administered percutaneously killed all guinea pigs in 24 hours, while 0.25 ml of a 35% aqueous solution was lethal to half of the animals during the same time.

Ocular irritation studies by Guess showed that undiluted 2-chloroethanol caused a transient clouding of the cornea, iritis, and inflammation of the conjunctiva. This reaction sequence became diminished at 1/5 aqueous dilution of 2-chloroethanol, particularly at 72 hours after application. Studies by Lawrence et al. (1971a) confirmed the eye irritation effects of the undiluted compound, and found that aqueous solutions of 1.25% (v/v) failed to produce this irritation. Guess (1970) found mucosal tissue to be more sensitive to 2-chloroethanol than eye or muscle tissues since 1/100 aqueous dilutions produced mild, transient signs of irritation in rabbit penile mucosa. McDonald et al. (1972) tested the ocular toxicity of 2-chloroethanol in rabbits and found maximum nontoxic aqueous concentrations to be 1% for topical application and 0.5% for intraocular administration. These investigators noted that intraocular toxicity at

2% or higher concentrations produce irreversible changes in opacity of the cornea and lens.

Lawrence et al. (1971a) observed dose-related depression of systolic and diastolic blood pressure in rabbits injected i.v. with 2-chloroethanol at doses of 606 mg/kg and higher. Death followed in 1 to 2 hours due either to CNS effects or direct cardiotoxicity. At this dose, sciatic nerve conduction was impaired and skeletal muscle contraction eventually blocked, with fasciculation observed.

Drug interactions between 2-chloroethanol and acetaminophen were studied by Balazs (1976). Pretreatment of rats s.c. with 10 mg/kg of 2-chloroethanol promoted liver necrosis by 200 mg/kg of acetaminophen. This hepatotoxicity was seen only with the combination of agents. Reduction of liver glutathione reserves by chloroethanol lowers the capability of the liver to detoxify metabolites that produce irreversible damage (Balazs, 1976).

2,2,2-Trifluoroethanol

Acute toxicity data for 2,2,2-trifluoroethanol are summarized in Table 14. Airaksinen (1968) noted that mice given a median lethal dose (158 mg/kg) of 2,2,2-trifluoroethanol interperitoneally showed initial "drunkenness," followed 24 hours later by tremor, stiffness, difficulty in moving, and death. After a dose of 250 mg/kg, analysis of the liver 18 hours after injection showed a marked decrease in lactate content while tissue citrate values showed little effect. A block of glycolytic rather than Krebs cycle metabolism was indicated. Rosenberg et al. (1970), after administering 200 mg/kg of 2,2,2-trifluoroethanol i.p. to mice, noted decreased liver ATP levels, increased ADP, decreased ATP/ADP ratio, and decreased total glycogen content. This glycolytic inhibition occurred within 5 hours and continued until the death of the animal, i.e., up to several days. Further work by this group (Rosenberg, 1971) indicated that

Table 14. Acute Toxicity of Trifluoroethanol

Route	Sex	Species	Strain	LD ₅₀	Reference
I.v.	M	mouse	Swiss	250 mg/kg	Airaksinen, 1968
Oral	M	mouse	Swiss	366 mg/kg	Blake et al., 1969
I.p.	M	mouse	Swiss	195 mg/kg	Rosenberg, 1971
I.p.	M	mouse	Swiss	100 mg/kg	Rosenberg, 1971
Ihl.	M	mouse	Swiss	85 ppm/10 min*	Rosenberg, 1971
Oral	M	rat	Sprague-Dawley	240 mg/kg	Hazelton Labs, 1965
Ihl.	M	rat	Sprague-Dawley	550 ppm/360 min*	Hazelton Labs, 1965
Dermal	M,F	rabbit		1680 mg/kg	Hazelton Labs, 1965
Oral		dog		100-200 mg/kg	Johnston et al., 1974

* LC₅₀

LD₅₀ levels of 2,2,2-trifluoroethanol given i.p. to mice produced significant ($p < 0.01$) reduction in liver glutathione (12 hrs.) and erythrocyte glutathione (24 hrs). Following a median lethal dose (200 mg/kg), reduced liver glutathione levels were observed, which recovered by 24 hours. This pattern was also observed with liver glucose-6-phosphate dehydrogenase activity, which showed maximal inhibition 12 hours after chemical injection (200 mg/kg).

Blake et al. (1969) found that median lethal doses of 2,2,2-trifluoroethanol (350 mg/kg, i.p.) administered to mice produced symptoms after a latent period of five hours. These symptoms included salivation, lacrimation, erythema (face and ears), tremors, labored respiration, and hyperreflexia. Dogs injected with 400 mg/kg showed immediate violent vomiting, hind leg ataxia, and bloody diarrhea. Eighteen to 24 hours later the animals were still lethargic, had persistent tremors, and labored, rapid breathing.

Hazleton Laboratories (1965) conducted a series of acute toxicity studies with rats and rabbits for Halocarbon Products Corp. Oral administration of a median lethal dose (300 mg/kg) of 2,2,2-trifluoroethanol to rats produced symptoms of marked depression, salivation, bloody lacrimation, labored respiration, tremors, ataxia, sprawling of the limbs, and vasodilation of the ears, feet, and tail. Necropsy showed marked congestion of the lungs, liver, kidneys, and adrenals. Acute dermal application (abraded skin) to rabbits (1385 mg/kg) produced symptoms similar to those just described in rats, as well as depression of righting and placement reflexes. Pathology showed congestion and/or hemorrhage of the lungs, congested kidneys, pale colored liver, spleen and kidneys (one animal). Slight erythema was seen at lower 2,2,2-trifluoroethanol doses after dermal application (138 mg/kg). Single application of 0.1 ml of undiluted 2,2,2-trifluoroethanol into the

conjunctival sack of rabbits followed by aqueous irrigation, produced severe eye irritation. Conjunctivitis, iritis, and corneal opacity were seen. Sodium fluorescein staining showed corneal damage. Some recovery (2/9) from chemosis, erythema, and corneal opacity was seen by days 7 to 14, but was not observed in those rabbit eyes which were not irrigated after 2,2,2-trifluoroethanol treatment.

Acute inhalation studies with rats (Hazleton Laboratories, 1965) indicated that after exposure to 350 ppm 2,2,2-trifluoroethanol for six hours animals showed marked depression and a hunched position. Following exposure, depression continued for five days, piloerection and sneezing were observed, and eye irritation and bloody nasal discharge were noted. Necropsy showed pulmonary congestion (3/10) and severe kidney congestion (2/10). At a concentration of 500 ppm ($\sim$ LC₅₀) lung surfaces showed discoloration and some instances of pinpoint gray-yellow nodes. Blake et al. (1967) determined an LC₅₀ concentration of 85 ppm for mice exposed 10 minutes. Based on this work a threshold limit value (TLV) between that of carbon tetrachloride (10 ppm) and trichloroethylene (100 ppm) was proposed by Blake et al. for 2,2,2-trifluoroethanol.

2-Bromoethanol

2-Bromoethanol was tested for toxicity in male ICR mice and found to have an approximate LD₅₀ level of 120 mg/kg by intraperitoneal injection (Dillingham et al., 1973). This level is comparable to that found for 2-chloroethanol given intraperitoneally to mice (LD₅₀, 120 mg/kg).

2-Fluoroethanol

2-Fluoroethanol was more toxic for rats than bromoethanol, showing an LD₅₀ of 20 mg/kg following i.p. administration. Table 15 summarizes the acute toxicity of 2-fluoroethanol.

Table 15. Acute Toxicity of 2-Fluoroethanol

Route	Sex	Species	Strain	LD ₅₀	Reference
I.p.		rat		5 mg/kg	Chenoweth, 1949
S.c.		rat		2-3 mg/kg	Foss, 1948
Oral		rat		2.5 mg/kg	Kalmbach, 1945
I.p.	M	rat	Sprague-Dawley	1.75 mg/kg	Peterson et al., 1968
I.p.		mouse		10 mg/kg	Ward and Spencer, 1947
S.c.		mouse		15 mg/kg	Pattison, 1953
I.v.		dog		0.05-0.07 mg/kg	Chenoweth, 1949
I.v.		monkey	Rhesus	4 mg/kg	Chenoweth, 1949
I.p.		guinea pig		0.4 mg/kg	Hutchens et al., 1949
S.c.		rabbit		0.3 mg/kg	Hutchens et al., 1949
Ihl.		mouse		419 ppm/10 min.*	OSRD, 1946
Ihl.		monkey		572 ppm/10 min.*	OSRD, 1946
Ihl.		dog		3 ppm/10 min.*	OSRD, 1946
Ihl.		cat		13 ppm/10 min.*	OSRD, 1946
Ihl.		rabbit		10 ppm/10 min.*	OSRD, 1946

*LC₅₀

2,3-Dichloro-1-propanol

Smyth and Carpenter (1948) evaluated the toxicity of 2,3-dichloro-1-propanol in rats and determined an oral LD₅₀ of 90 mg/kg. Inhalation of 500 ppm 2,3-dichloro-1-propanol for four hours was lethal to two of six rats. Application of this compound to intact rabbit skin (one day with rubber cuff) showed significant absorption, since 270 mg/kg produced 50% mortality. Eye injury tests of 2,3-dichloro-1-propanol showed damage graded as 5 on a scale of 1 to 10.

2,3-Dibromo-1-propanol

2,3-Dibromo-1-propanol is lethal to mice when administered intraperitoneally at 125 mg/kg (National Institute for Occupational Safety and Health, 1977).

Trichloroethanol

Acute toxicity data for trichloroethanol are summarized in Table 16. Whether liver toxicity is produced by inhalation of trichloroethylene vapors has been a subject of debate (Joron et al., 1955), since this compound shows moderate liver effects. Kylin et al. (1963) studied fatty changes in the liver following a single four-hour exposure of albino mice to trichloroethylene vapor. Moderate fatty infiltration was histologically confirmed three days after exposure to 3200 ppm trichloroethylene. No increase in total extractable liver fat or serum levels of ornithine carbamoyl transferase was shown. On the basis of these fatty infiltration studies, relative hepatotoxic effects for trichloroethylene, tetrachloroethylene, and chloroform were assessed at the ratios of 1:10:20, respectively.

Inhalation studies in rats (Smyth and Carpenter, 1969) indicated that a single four-hour exposure to 500 ppm of trichloroethanol vapor killed one of six animals.

Table 16. Acute Toxicity of Trichloroethanol

Route	Sex	Species	Strain	LD ₅₀	Reference
Oral		rat		~600 mg/kg	Lehmann and Knoeffel, 1938
I.p.		rat		~400 mg/kg	Lehmann and Knoeffel, 1938
I.v.		mouse		201 mg/kg	NIOSH, 1977
I.v.		rabbit		~60 mg/kg	Lehmann and Knoeffel, 1938

Table 17. Acute Toxicity of 2-Chloro-1-propanol

Route	Sex	Species	Strain	LD ₅₀	Reference
Oral	M	rat	Wistar	220 mg/kg	Smyth et al., 1941
Oral		guinea pig		720 mg/kg	Smyth et al., 1941
Ihl.		rat		~500 ppm*	Smyth and Carpenter, 1969
Dermal		rabbit		480 mg/kg	Smyth and Carpenter, 1969

* LC₅₀

Lehmann and Knoeffel (1938) investigated the effects of trichloroethanol and tribromoethanol in anesthetized dogs and in the isolated, perfused rabbit heart. Both compounds produced respiratory depression (50 mg/kg) in dogs, with tribromoethanol showing greater depression (not corrected for molecular weight differences). Circulatory effects included slowing of heart rate and fall in arterial pressure (dogs, perfused rabbit heart), indicating effects on both the CNS vasomotor centers and directly on the heart. Trichloroethanol and tribromoethanol in 3 percent aqueous solution applied topically to rabbit eyes produced moderate conjunctivitis but had no effect on pupil size.

2-Chloro-1-propanol

Acute toxicity data for 2-chloro-1-propanol are summarized in Table 17. Smyth and Carpenter (1969) observed an LD₅₀ of 220 mg/kg for 2-chloro-1-propanol administered orally to male Wistar rats. This compound is less toxic by the oral route than either 2-chloroethanol or 3-chloro-1,2-propanediol.

c. Sub-Chronic Toxicity

3-Chloro-1,2-propanediol

Kirton et al. (1970) observed toxic symptoms such as lack of coordination and muscular weakness in Rhesus monkeys (*Macaca mulatta*) orally dosed with 3-chloro-1,2-propanediol at the rate of 30 mg/kg/day for 6 weeks. Hemorrhage (site unspecified) and depression were noted in the fifth and sixth weeks. Blood tests showed severe anemia, leukopenia, and thrombocytopenia, implicating bone marrow damage by the drug. Necropsy on two of six monkeys showed hemorrhage, pneumonia, enteritis, pleurisy, and peritonitis. No microscopic examination of organs was described. In a preliminary report covering 110 days of observation, Jackson (1977) observed no apparent adverse effects in dogs that received 50 oral doses of double-distilled 3-chloro-1,2-propanediol at 30 mg/kg/day followed by another 50 doses at 60 mg/kg. Samojlik and Chang (1970)

observed paralysis and impaired reflexes in Sprague-Dawley rats treated s.c. with 40 mg/kg/day 3-chloro-1,2-propanediol (purity not described) for 20 days.

2,2,2-Trifluoroethanol

Blake et al. (1969) noted that mice treated intraperitoneally with 100 mg/kg of 2,2,2-trifluoroethanol daily for 18 days failed to gain weight while controls increased by 40%. Rosenberg and Wahlstrom (1971) observed fat accumulation in liver cells with electron microscopy after 2,2,2-trifluoroethanol (160 mg/kg) was given intraperitoneally, but was unable to show liver cell necrosis after administering the compound every second day for two weeks. Stevens et al. (1975) exposed rats, mice, and guinea pigs to a series of concentrations of halothane for a constant 35-day period. At 1/100 to 1/200 of the maximum allowable concentration (70 to 150 ppm) all species showed an increased incidence of degenerative hepatic lesions, including granular and vacuolar degeneration, zonal centrilobular lipidosi, focal lipidosi, and focal necrosis.

Hazleton Laboratories (1975) studied the effects of 2,2,2-trifluoroethanol inhalation on rats (5 days/wk, 6 hours/day) for four weeks. Mean testis weight decreased in rats exposed at the level of 150 ppm. Microscopic examination showed hypospermatogenesis in these rats. Occasional fusion bodies were seen in the seminiferous tubules of rats exposed at 50 ppm. Regeneration and normal spermatogenesis in "many" seminiferous tubules was seen after 150 ppm in a subsequent 57-day recovery period. Rats exposed to 50 and 150 ppm 2,2,2-trifluoroethanol showed functional impairment of reproductive capability as determined by decreased conception rates, decreased number of corpora lutea, decreased implantation sites, decreased live fetuses, increased pre-implantation losses and increased post-implantation losses. Effects were

attributed mainly to hypospermatogenesis produced at these two concentrations. Extensive pathology of other organs in rats exposed to 50 and 150 ppm 2,2,2-trifluoroethanol showed no histomorphologic differences from controls (Hazleton Laboratories, 1975).

1-Chloro-2-propanol

Gage (1970) conducted a number of inhalation tests with rats on the toxicity of repeated exposures to 1-chloro-2-propanol. At 1000 ppm, 1-chloro-2-propanol induced one death after two 6-hour exposures, 3 days apart. Pathology revealed edema of the lungs, inflammatory exudate of the lungs, and swelling and vacuolization of liver cells. A concentration of 250 ppm produced signs of lethargy, irregular weight gain, and congestion of the lungs with perivascular edema; 100 ppm produced no toxic symptoms, but pathology indicated some edema of the lungs. The material used in these inhalation studies was not purified and therefore could contain as much as 25% of the isomer 2-chloro-1-propanol.

Trichloroethanol

Kylin (1965) treated female albino mice, four hours daily for six days a week, with trichloroethylene vapor (1600 ppm). Increased fatty degeneration of the liver was noted relative to controls. This deleterious effect increased through two weeks exposure and then declined after four and eight weeks of trichloroethylene treatment. Total extractable fat from the liver of trichloroethylene treated animals showed a small increase ($p < 0.01$). No cirrhosis or liver cell necrosis was seen, and no kidney lesions were observed.

2-Chloroethanol

Oral feeding of 4.5 to 180 mg of 2-chloroethanol daily to rats induced fatalities in all animals (Ambrose, 1950). Deaths occurred in 7 to 49 days.

Oser et al. (1975) conducted feeding studies in rats, dogs, and monkeys for 90 days. Rats dosed at 67.5 mg/kg/day showed decreased food intake, decreased body weight, and 70% fatalities. Necropsies indicated a high incidence of myocarditis and fatty liver in short term survivors. Dogs fed 13 to 18 mg/kg/day of 2-chloroethanol failed to gain weight, nor did monkeys given 45-63 mg/kg daily. There was some lowering of the dogs' hemoglobin and hematocrit ranges by week six, and recovery by week 12. In other studies, intraperitoneal administration of 2-chloroethanol to rats was performed three times per week for 90 days, and daily for 30 days (Lawrence et al., 1971b). The intermittent schedule produced no deaths in rats dosed at 6.4 mg/kg or 12.8 mg/kg, but at 32 mg/kg six of 12 test animals died. With daily administration of 2-chloroethanol at 12.8 mg/kg, toxicity was seen after 30 days. At this level there was a slightly increased leucocyte count. Weight gain was poor in animals receiving toxic levels of drug, but no significant histopathological lesions were observed. Minden et al. (1969) found liver parenchymal lesions and serum enzyme changes in rabbits given 30 mg/kg of 2-chloroethanol daily for five days by intravenous injection.

2-Chloroethanol (10 mg/kg, s.c.) on three consecutive days caused impairment in a conditioned reflex test in cats (Balazs, 1976).

Subacute toxicity tests in rats (~65 mg/kg) with 2-chloroethanol have shown myocardial lesions (route and duration of exposure not specified) (Balazs, 1976).

Toxicity induced by repeated one-hour inhalations of 2-chloroethanol at 2 ppm in rats has been reported by Ambrose (1950). Paralysis in "some" rats and deaths were observed, but no quantitation was presented.

Dermal application of 6.25% aqueous 2-chloroethanol to intact skin in rats was fatal when repeated twice within three days (Ambrose, 1950). Four dermal applications of 0.5 ml of undiluted compound to rabbits over four days produced fatalities, while a single application at this concentration did not.

Oral administration of 2-chloroethanol to rats at 70 mg/kg daily for one week increased serum amylase and decreased quinine-resistant lipase (Strusevich and Ekshtate, 1973). Inhalation of 36 to 42 ppm 2-chloroethanol (duration not specified) decreased serum amylase and cholinesterase, and increased serum lipase activity. Both hepatic and pancreatic toxicity have been inferred from these results.

Taylor (1969) investigated the toxicity of 2-chloroethanol in feeding studies with rats, dogs, and monkeys. Results of feeding studies (26 weeks) with laboratory rat chow containing 2-chloroethanol cannot be evaluated since less than 20% of the desired 2-chloroethanol concentration was found after chemical analysis of seven-day old feed. Daily feeding of rats by stomach tube for 90 days at 67.5 mg/kg resulted in 70% deaths in the first three weeks. Pathology showed abnormal color of the liver, gastrointestinal tract reddening, and hemorrhagic adrenals and pituitary. Microscopic examination showed fatty changes of the liver, colloid depletion of the thyroids, congestive changes in the thymus, and subacute myocarditis. Those animals surviving this level of 2-chloroethanol showed decreased weight gain. Oral feeding studies (stomach tube) with rats for 23 weeks cannot be interpreted since the concentration of 2-chloroethanol was changed twice during the course of the investigation. Emesis produced by 2-chloroethanol in feeding studies with dogs, and subsequent alterations in chemical levels imposed by the investigators to compensate for this loss, make

results from these studies uninterpretable. Studies with monkeys fed 2-chloroethanol by stomach tube indicate some effects of the chemical on reducing the weight of the testes. No dose response data were presented, and the small size of the groups tested indicates that this was a preliminary study.

d. Chronic Toxicity

2-Chloroethanol

Ten groups of five rats each that were fed 2-chloroethanol for 220 days began to show decreased weight gain at 0.16% dietary concentration of compound (~45 mg/kg) (Ambrose, 1950). Pathology of these animals showed no abnormal histopathology in organ sections from the heart, lung, liver, kidney, spleen, adrenal, pancreas, intestine, bladder, testis, and thyroid.

Injection of rats twice weekly for one year indicated that 2-chloroethanol given at 10 mg/kg subcutaneously was tolerated without major weight loss or gross organ pathology (Mason et al., 1971). However, mild changes in liver, kidneys, heart, and lungs were noted but not quantitated. Pneumonia was seen in some rats, but the rate was not significantly different from that seen in controls.

Kovyazin (1971) has reported central nervous system effects and liver injury in rats exposed to 3 ppm 2-chloroethanol by chronic inhalation.

Strusevich et al. (1972) found increases in blood lecithin and cholesterol of rats subjected to either 0.3 ppm or 3 ppm chloroethanol for four months. Recovery was seen in two weeks after the low dose inhalation.

3-Chloro-1,2-propanediol

Purified 3-chloro-1,2-propanediol was given orally, 5 days/week, at 50 mg/kg to male rats (Jackson, 1977). All animals survived this treatment regimen for one year, and 15 of 20 rats were alive two years after administration of the first dose ($\sim 1/2$ of the LD_{50}). This preliminary study indicates that the pure compound is less toxic than previously reported.

e. Reproductive Effects

3-Chloro-1,2-propanediol

Since early reports (Coppola, 1969; Ericsson, 1968) of the antifertility effects of 3-chloro-1,2-propanediol indicated it had potential as a reversible, post-testicular agent, much research on this application of 3-chloro-1,2-propanediol has ensued. Coppola (1969) showed that at a level of 5 mg/kg daily (oral) for 12 days, sterility could be induced in male Wistar rats. Fertility was partially restored immediately after compound withdrawal. Higher levels of 3-chloro-1,2-propanediol (25 mg/kg) produced spermatogenic arrest at the level of the primary spermatocyte. Samojlik and Chang (1970) showed that 3-chloro-1,2-propanediol administered s.c. at 15 mg/kg daily for six days in rats caused a marked reduction in sperm motility and a significant decrease of oxygen uptake by sperm cells. Ericsson (1970) determined that minimal amounts of 3-chloro-1,2-propanediol needed to produce permanent lesions in the caput epididymis of the rat were 35 mg/kg (daily oral doses) or 45 mg/kg (single oral dose). Formation of spermatocoeles caused irreversible blockage of the caput, with subsequent degeneration of the germinal epithelium. Reversible antifertility effects with 3-chloro-1,2-propanediol have been observed in certain species (rat, ram, boar, monkey, guinea pig) but not in others (mouse, rabbit) (Ericsson et al., 1971). The biochemical mechanism of action in sperm is the

inhibition of formation of 3-phosphoglycerate from glyceraldehyde-3-phosphate (Mohri et al., 1975). Mashford and Jones (1978) tested 3-chloro-1,2-propanediol phosphate in vitro and showed it to be a strong competitive inhibitor of glyceraldehyde-3-phosphate dehydrogenase. Both epichlorohydrin and glycidol, which are effective anti-fertility agents in vivo, have no effect on this enzyme in vitro, nor does 3-chloro-1,2-propanediol. All three agents probably share the common end metabolite, 3-chloro-1,2-propanediol phosphate, in order to inhibit sperm glycolysis.

Dixit and Lohiya (1976) observed inhibition of new spermatogonia in the testes of male rats and gerbils given 3-chloro-1,2-propanediol orally (gerbils: 20 mg/kg for 50 days; rats 25 mg/kg for 24 days). This testicular effect produced changes in the anterior pituitary resembling those produced by castration in controls. A rise in the activity of gonadotrophic cells after 3-chloro-1,2-propanediol treatment was indicated by an increased percentage of pituitary basophilic cells.

f. Mutagenicity

3-Chloro-1,2-propanediol

Glycidol, a possible 3-chloro-1,2-propanediol metabolite (see Figure 7), has been shown to be mutagenic in Drosophila, Hordeum, and Neurospora test systems (Loveless, 1966), but was found noncarcinogenic after long term painting of mouse skin by Van Duuren et al. (1967). Jackson et al. (1970) found glycidol to be negative in the dominant lethal assay for mutation effects; similar results were reported earlier (Jones et al., 1969) for 3-chloro-1,2-propanediol.

2-Chloropropanol

2-Chloropropanol, a residue found in foodstuffs after propylene oxide sterilization, was tested in the Ames system for mutagenicity

(Rosenkranz et al., 1975). The compound tested was 75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol, and was incorporated directly into the agar overlay. Tester strain TA 1530 showed increased mutations (base substitution) while strain TA 1538 was unaffected (frameshift mutation sensitive). A graded increase in the number of revertants was seen at concentrations of 2.2 to 22 mg/plate in the absence of liver S-9 mix activation.

1,3-Dichloro-2-propanol

Testing of 1,3-dichloro-2-propanol in the Ames mutagenicity assay was carried out (Gold et al., 1978) because this compound is a suspected metabolite of the flame retardant Fyrol FR2. This compound (50 to 1000 µg/plate) was found to increase mutation frequency in tester strain TA 100 when phenobarbital-induced rat-liver homogenate was present. However, this increase in the number of revertants was not shown when Aroclor (PCB)-induced rat-liver homogenate (S-9 mix) was used for activation. The authors caution that several liver preparations from different species and with various inducers should be tried when evaluating mutagenicity in the Ames system.

2,3-Dibromo-1-propanol

Investigation of 2,3-dibromo-1-propanol for mutagenicity was initiated by the finding (St. John et al., 1976) that this compound could be found in the urine of rats treated dermally with the flame retardant (and mutagen) Tris. Blum and Ames (1977) reported that 2,3-dibromo-1-propanol (50 µg/plate) increased the mutation rate in tester strain TA 100 when Aroclor S-9 activation mix was included. Prival et al. (1977) tested this compound in the Ames assay with tester strains TA 1535 and TA 1538. The results showed that when 0.1 or 1 ml of compound was applied to the TA 1535 plates, the mutation frequency was increased (with Aroclor S-9 mix). This activity was not seen in TA 1538 plates, with or without S-9.

2,2,2-Trifluoroethanol

Waskell (1978) studied the effects of 2,2,2-trifluoroethanol in the Ames assay system (strains TA 98 and TA 100) and found no increased number of revertants at 69 mg/plate, either with or without S-9 enzyme mix added. Baden et al. (1978) reported that 2,2,2-trifluoroethanol was not mutagenic to tester strains TA 1535, TA 1537, TA 98, and TA 100 when assayed in liquid suspension. Concentration of drug and presence or absence of S-9 mix was not specified.

Trichloroethanol

Waskell (1978) examined the mutagenicity of 2,2,2-trichloroethanol (69 mg/plate) in the Salmonella system developed by Ames. The microsomal enzyme preparation (S-9 mix) was obtained from Sprague-Dawley rats induced with both Aroclor and phenobarbital. Trichloroethanol was not mutagenic either with or without the microsomal enzyme mix. Chloral hydrate (1 to 10 mg) produced moderate mutagenic activity (~100 revertants above controls) either with or without S-9 mix; this compound rapidly produces trichloroethanol in vivo (see Figure 8).

Trichloroethylene has been shown to be mutagenic in the Ames assay (Simmon, 1977), particularly after addition of S-9 mix (rat, mouse). In vivo metabolism of trichloroethylene will produce trichloroethanol (see Figure 8). The trichloroethylene used may contain sufficient epichlorohydrin impurity to account for the observed effect.

2-Chloroethanol

Investigation of the effects of 2-chloroethanol in the Ames test indicated that this compound (5-20 μ l/plate) induced an increased number of revertants in tester strains TA 1530 and TA 1535, but not in strain TA 1538 (Rosenkranz et al., 1974). 2-Chloroethanol (10 μ l) also showed some

preferential inhibition of DNA polymerase deficient E. coli growth. Bartsch et al. (1975) showed that 2-chloroethanol (8 mg/plate) produced increased revertants in strains TA 1530 and that this frequency doubled if S-9 enzyme mix was added. McCann et al. (1975) found that 1 to 5 mg 2-chloroethanol induced increased mutations in TA 100, primarily after addition of S-9 mix for activation. Chloroacetaldehyde, a chloroethanol metabolite (see Section C.1), was several hundredfold more effective in inducing mutations, on a molar basis. Similar potent mutagenicity of chloroacetaldehyde monomer hydrate and chloroacetaldehyde in Salmonella TA 100 and in a repair deficient Bacillus subtilis strain was reported by Elmore et al. (1976). Rannug et al. (1976) found that 1 M 2-chloroethanol was weakly mutagenic (without activation) for TA 1535 strain Salmonella. As little as 0.5 mM chloroacetaldehyde produced an increase in revertants in this same test system.

The haloalcohol series 2-bromoethanol, 2-iodoethanol, and 2-chloroethanol was investigated for relative mutagenicity. Rosenkranz et al. (1974) reported that bromoethanol was most mutagenic (strains TA 1530 and TA 1535) followed in order by iodoethanol and chloroethanol. Investigation of the same series for mutagenicity with *Klebsiella pneumoniae* (Voogd and Vet, 1969) showed that iodoethanol was most mutagenic, followed in order by bromoethanol and chloroethanol. All the haloalcohols were compared at the same concentration in the *Klebsiella* study, but not in the *Salmonella* study.

In vitro reaction of chloroethanol, bromoethanol, and iodoethanol for varying time periods with calf thymus DNA has been shown to increase the DNA buoyant density (Rosenkranz et al., 1974), indicating mutation potential following physical interaction.

Mutation induction by 2-chloroethanol was studied by Huberman et al. (1975) in Chinese hamster V79 cells. Using 8-azaguanine resistance and ouabain resistance as genetic markers, 2-chloroethanol did not increase the mutation frequency. Chloroacetaldehyde at 6.4 μM concentration was mutagenic, but this concentration also reduced the cloning efficiency of treated cells. In an assay system measuring forward mutations and gene conversions in yeast (Loprieno et al., 1977), 2-chloroethanol was not found to be mutagenic. Chloroacetaldehyde was weakly mutagenic, producing a 2 to 7 fold increase at 6 to 12.5 μM concentration.

Isakova et al. (1971) reported that rats exposed by inhalation to 0.3 to 30 ppm 2-chloroethanol for three months showed bone marrow abnormalities. The frequency of aneuploid cells increased, and chromatid type aberrations as well as prolonged mitosis was observed in the first two months of exposure. This pattern of abnormal cells subsequently diminished with time, since the statistical significance of chromosomal changes at six months is less than that seen at two months.

g. Teratogenicity

2-Chloroethanol

2-Chloroethanol was administered to pregnant mice from the sixth to the sixteenth day of gestation by Courtney and Andrews (1977) in an unpublished study. With chloroethanol given by gastric intubation, a dose level of 150 mg/kg was lethal to 75% of the mice. At the concentration of 100 mg/kg, 2-chloroethanol caused decreased maternal weight gain, decreased fetal body weight, and decreased fetal liver weight. The number of implants or the number of live fetuses was not affected. No results were reported on the survivors of the high dose (150 mg/kg) regimen; this test group (8 animals) was significantly smaller than the others evaluated (18 animals).

Verrett (1974) found an increased number of fetal abnormalities in chicks treated at the embryo stage with 2-chloroethanol (injection into the air cell). Of these abnormalities, the most frequently seen was anterior hydrophthalmos. However, most of the teratogenic effects were noted at 2-chloroethanol concentrations approaching or exceeding an LD₅₀ level. In addition, the control used in the experiment (H₂O) may not be adequate. Ethanol, at an equimolar concentration, probably would have presented a more valid comparison, since nonspecific membrane effects at this concentration could result from the lipophilic activity of the compound.

h. Carcinogenicity

2-Chloroethanol

In a long term study of Fischer weanling rats injected twice weekly for a year with 2-chloroethanol (10 mg/kg, s.c.), Mason et al. (1971) found that the incidence of pituitary adenomas was increased. Untreated controls showed 1/120 incidence while 2-chloroethanol treated rats had an incidence of 7/200, all occurring in the 100 female test group.

Balazs (1976) has reported on a study in which rats were injected subcutaneously with 10 mg/kg chloroethanol twice a week for a year, then observed for an additional six months. No increased tumor incidence was seen in this preliminary study.

Homburger (1968) in an unpublished study administered 1.2 mg 2-chloroethanol subcutaneously to one hundred C57BL/6 mice (male), transferred minced skin pieces five weeks after the 2-chloroethanol injections (to shorten tumor latency) into mice from the same litter, and evaluated these recipients, 18 weeks later for tumor incidence. No increased tumor incidence

was observed in the 2-chloroethanol-treated animals. The relevance of this system for assessing carcinogenicity has not been shown. Also, since the number of injections of 2-chloroethanol and their scheduling was not reported, it is not possible to assess the significance of these negative results.

In another part of this study designed to evaluate 2-chloroethanol effects in producing lung adenomas, Homburger (1968) injected female CF1 mice with either one or seven monthly i.v. doses of 1.2 mg of compound. Mice injected with a single intravenous dose did not show an increase in adenomas over controls at 28 weeks. Those animals receiving multiple doses did show a slight increase in adenomas (5/18 versus control 2/18), but the high spontaneous rate of this tumor in this strain and the small number of animals tested make interpretation of this increase difficult.

Trichloroethanol

Trichloroethanol is formed rapidly in vivo following inhalation of trichloroethylene (Ertle et al., 1972). Unpublished results from Stanford Research Institute have indicated that trichloroethylene is weakly mutagenic after metabolic activation (Simmon, 1977). Therefore, consideration of data on trichloroethylene effects may be relevant in assessing trichloroethanol.

The results of a carcinogenicity bioassay of trichloroethylene by the National Cancer Institute (1976) indicated that this compound produced hepatocellular carcinomas in mice after high-dose feeding for 78 weeks. Loprieno, in a letter to the Manufacturing Chemists Association (Clark, 1978) stated that the small amount of epichlorohydrin impurity (0.09%) present in the trichloroethylene used can produce positive results in the Ames assay; testing of pure trichloroethylene did not show any mutagenic activity.

Caution is therefore advised in interpreting positive trichloroethylene carcinogenicity data, unless the sample has been shown to be free of epichlorohydrin.

2. Toxicity and Effects on Other Vertebrates

No data are available concerning effects of the haloalcohols on other vertebrates.

3. Toxicity and Effects on Invertebrates

2-Chloroethanol

2-Chloroethanol has been widely used as an acaricide. Mites, which have been reported to be sensitive to 2-chloroethanol, include spider mites, hawthorn mites, and fruit tree mites (Margzhanyan et al., 1971). Sukhoruchenko and Tolstova (1974) have reported on the sensitivity of the *Chrysopa* species to 2-chloroethanol toxicity.

D. Toxicity and Effects on Plants

The herbicidal activity of several haloalcohols was studied by Poignant and Richard (1958). 2-Chloroethanol and 2,3-dibromo-1-propanol destroyed flax and white mustard plants when applied at the rate of 40 kg/hectare. At this same concentration 1-chloro-2-propanol, 1,3-dichloro-1-propanol, and 3-chloro-1,2-propanediol were without effect.

2-Chloroethanol

2-Chloroethanol has been widely used to increase the rate of sprouting of potatoes, probably by increasing amylase levels during the germination period (Arai, 1954). The opening of dormant grapevine buds has also been promoted with 2-chloroethanol (Alleweldt, 1960). Wheat seeds soaked in 2-chloroethanol have shown an increased resistance to high soil salt concentrations (Miyamoto, 1963). Vegetative growth of the Zinna has been impaired by this compound, with chlorosis of the leaves and stems observed (Alberte, 1970).

E. Toxicity and Effects on Microorganisms

2,2,2-Trichloroethanol

Prins and Seekles (1968) studied the effect of 2,2,2-trichloroethanol on rumen metabolism in cattle. 2,2,2-Trichloroethanol decreased the breakdown of cellulose, probably through direct action on rumen microorganism metabolism.

F. In Vitro and Biochemical Studies

2,2,2-Trifluoroethanol

Rosenberg et al. (1970) determined that 10^{-4} M to 10^{-6} M 2,2,2-trifluoroethanol added to mouse liver homogenates inhibited anaerobic glycolysis by about 30%. Incubation of creatine phosphokinase with trifluoroethanol did not block enzyme function, but addition of the -SH group reactive metabolite trifluoroacetaldehyde hydrate did produce a dose-dependent inhibition (Airaksinen, 1970). Rosenberg and Wahlstrom (1971) were unable to inhibit glucose-6-phosphate dehydrogenase activity in vitro by the addition of either 2,2,2-trifluoroethanol or trifluoroacetaldehyde hydrate. Marsh et al. (1977) showed in vitro degradation of hepatic P-450 cytochrome with microsomes, fluroxene, and NADPH. This cytochrome destruction correlated linearly with 2,2,2-trifluoroethanol generated in the in vitro system under varying conditions of induction. Rosenberg (1971) demonstrated that 2,2,2-trifluoroethanol at 0.1 mM to 50 mM did not inhibit human fibroblast growth in vitro, while the acetaldehyde hydrate metabolite did so in a dose dependent fashion.

Ishii and Corbascio (1971) were unable to show effects of 1 mM 2,2,2-trifluoroethanol or trifluoroacetate on hepatoma cell uridine uptake, thymidine uptake, or leucine and acetate uptake. Halothane, which may produce trifluoroethanol after metabolism, did increase acetate uptake in these cells indicating stimulation of lipid synthesis. At a concentration of 100 mg/100 ml, halothane was cytotoxic to both hepatoma and Hela cell lines.

Blair and Vallee (1966) studied the effects of 2,2,2-trifluoroethanol on purified human liver alcohol dehydrogenase. At pH 9.3, 50% inhibition of enzyme activity was produced by a 5×10^{-4} M solution of the drug. Blake et al. (1969) found that 2,2,2-trifluoroethanol inhibited yeast alcohol dehydrogenase activity in a competitive manner (relative to ethanol) at pH 8.2.

Trichloroethanol

Krieglstein and Stock (1973) studied metabolic changes induced in the isolated perfused rat brain by trichloroethanol. At a concentration of 3.5 mM, trichloroethanol caused an accumulation of creatine phosphate, an increase in glucose concentration, and a decrease in glucose-6-phosphate levels ($p < 0.05$). The glucose increase after addition of trichloroethanol appears to be concentration dependent, and a mechanism involving inhibition of brain hexokinase has been proposed.

Ammon et al. (1967) administered trichloroethanol (i.v., 269 mg/kg) to white mice and determined the acetyl donating activity of liver acetyl coenzyme A in the presence of transacetylase. This high concentration of trichloroethanol produced ~10% reduction in liver coenzyme A activity. Tribromoethanol at a concentration near the LD₅₀ level, produced no reduction in liver coenzyme A activity.

Grüner et al. (1973) investigated EEG changes in the isolated, perfused rat brain after administering trichloroethanol. Trichloroethanol (1.5 to 5 mM) showed CNS depressant activity, with increasing concentration of chemical producing progressively fewer brain waves over 50 microvolt/sec amplitude. The EEG changes were complete in 10 minutes, indicating a rapid onset and short duration of action.

2-Chloroethanol

Feuer et al. (1977) investigated the effect of subcutaneous administration of 2-chloroethanol on rat liver microsomal drug metabolizing enzymes. Daily administration of 20 mg/kg of 2-chloroethanol for seven days to female rats produced a decrease in the activity of aminopyrine N-demethylase ($p < .05$); this same schedule in male rats produced decreases in coumarin 3-hydroxylase ($p < .05$) and aminopyrine N-demethylase activities (no statistics for the latter). No morphological changes in the liver were observed after this dosage schedule.

The inhibitory growth effects of 2-chloroethanol were investigated on an L cell culture, NCTC clone 929 (Dillingham et al., 1973). 2-Chloroethanol inhibited fibroblast growth by 50% at a concentration of $3 \times 10^{-3} \text{ M}$, while 2-fluoroethanol and 2-bromoethanol showed higher toxicity ($\text{LD}_{50} = 2 \times 10^{-2} \text{ M}$ and $2 \times 10^{-3} \text{ M}$, respectively). These same authors reported that 50% lysis of rabbit erythrocytes in isotonic saline is produced in one hour by 0.6 M 2-chloroethanol. Ethanol, in comparison, shows this activity at 2 M concentration. There was excellent correlation between this hemolytic effect and the fibroblast inhibitory effect, as well as a uniform relationship between the product of the in vitro toxicity concentration and water/octanol partition coefficient, versus the in vivo LD_{50} toxicity concentration. This suggests that the toxicity of the haloalcohols studied here is related to their membrane effects.

Osterman-Golkar et al. (1977) have investigated the alkylating potential of various vinyl chloride metabolites. Based on theoretical evaluations utilizing rate constants derived from reactions with model nucleophiles in vitro, alkylation by 2-chloroethanol has been concluded to be negligible. Hemoglobin histidine alkylation with both chloroacetaldehyde and chloroethylene

oxide has been estimated and the rate constants indicate that chloroacetaldehyde is several orders of magnitude less reactive than chloroethylene oxide at 37°C.

Blair and Vallee (1966) have shown that 2-chloroethanol is a substrate for human alcohol dehydrogenase in vitro. The rate of oxidation is 20% compared with ethanol as a substrate. 2-Fluoroethanol is oxidized at 10%, and 2-bromoethanol at 15%, of the natural substrate rate. Inhibition of alcohol dehydrogenase probably takes place via competition with ethanol as a substrate.

G. Effects on Environmental Quality

There was no information available concerning the effects of the selected haloalcohols on environmental quality.

H. Effects on Inanimate Objects

There was no information available concerning the effects of the selected haloalcohols on environmental objects.

IV. Current Regulations

A. Federal, State and Local Standards

1. Food, Drug, and Pesticide Authorities

Although none of the selected haloalcohols are applied as pesticides, or are directly added to food or drugs, some are metabolites of pesticides. Ethylene oxide and propylene oxide, which are fumigants for bulk food stuffs and sterilants for cosmetics, drugs, medical devices and single service items, yield the corresponding chlorohydrins and/or bromohydrins as metabolites. The Environmental Protection Agency and Food and Drug Administration have set tolerances for halohydrin content in various commodities, medical devices and other goods.

FDA tolerances for residual ethylene chlorohydrin (chloroethanol) in drugs and medical devices are as follows (Federal Register, 1978):

(Parts per million)

Drug product	Ethylene oxide	Ethylene chlorohydrin	Ethylene glycol
Ophthalmics (for topical use)	10	20	60
Injectables (including veterinary intramammary infusions)	10	10	20
Intrauterine device (containing a drug)	5	10	10
Surgical scrub sponges (containing a drug)	25	250	500
Hard gelatin capsule shells	35	10	35
<u>Medical device</u>			
<u>Implant:</u>			
Small (<10 grams)	250	250	5,000
Medium (10-100 grams)	100	100	2,000
Large (<100 grams)	25	25	500
Intrauterine device	5	10	10
Intraocular lenses	25	25	500
Devices contacting mucosa	250	250	5,000
Devices contacting blood (ex vivo)	25	25	250
Devices contacting skin	250	250	5,000
Surgical scrub sponges	25	250	500

Propylene oxide may be added to food starch. Propylene chlorohydrin limitations are 5 ppm for residues (Code of Federal Regulations, 1977a).

Ethylene oxide and propylene oxide may be applied as a fumigant to spices, whole grains, and other commodities including dried prunes, glace-fruit, gums, cocoa and processed nutmeats. The Environmental Protection Agency has established tolerances for propylene oxide (300 ppm) and propylene glycol (700 ppm) but not on propylene chlorohydrin (Code of Federal Regulations, 1977a). Ethylene oxide residue was established at 50 ppm, but no separate value was assigned for ethylene halohydrin (Code of Federal Regulations, 1977b).

2. Air and Water Acts and Other EPA Authority

The haloalcohols are not specifically regulated within the air, water, or resource conservation and recovery acts or any other Environmental Protection Agency authorities.

3. Occupational Safety and Health Administration

OSHA has set the TLV for chloroethanol (ethylene chlorohydrin) at 5 ppm maximum concentration for 8 hour exposure.

4. DOT, ICC, CG - Transport Regulations

None of the selected haloalcohols are listed by the DOT as hazardous materials (Code of Federal Regulations, 1977c).

5. Foreign Countries

Foreign standards on the selected haloalcohols include the following: suggested maximum chloroethanol in air for four hour exposure (Russian) is 0.5 mg/m^3 (Kovyazin, 1971); trichloroethanol in air at 100 ppm is a German standard which was considered too high (Linder, 1973); Russian occupational standard for the trichloroethanol is 1 ppm (Andrianov, 1971); proposed occupational standard of Romania for 1,3-dichloro-2-propanol is

3 ppm (0.005 mg/l) (Pallade et al., 1964); and atmospheric standard for tri-fluoroethanol in Russia is 2.45 ppm (10 mg/m³) (Nikitenko and Tolgskaga, 1969). Russia has set the maximum concentration of chloroethanol in reservoir water at 30.5 ppm (0.1 mg/l) (Semenova et al., 1971).

B. Consensus and Similar Standards

No information on consensus or other standards was found which differed from the information described above. ACGIH (1977) suggested the TLV (5 ppm) for occupational exposure to ethylene chlorohydrin (chloroethanol) which was adopted as the OSHA standard.

C. Current Handling Practices

1. Special Handling in Use

The selected haloalcohols require no special handling practices in their use. Sax (1964) listed chloroethanol (ethylene chlorohydrin), 1-chloro-2-propanol (propylene chlorohydrin), 1,3-dichloro-2-propanol, and trichloroethanol and suggested standard practices for handling and use of liquids. The areas of use should be equipped for moderate ventilation. Workers should exercise standard personal hygiene practices to avoid contact by dermal or inhalation routes. Rubber gloves are not effective, since some haloalcohols, e.g., chloroethanol, will pass through rubber (Lichtenwalter and Riesser, 1964).

The haloalcohols can hydrolyze to yield corrosive acids (in particular hydrolysis to HCl or to HBr). For this reason, Lichtenwalter and Riesser (1964) suggested that process equipment should be constructed of materials which will not be corroded by acid, such as glass, ceramics, high-silica iron, tantalum or "Hastelloy" alloys.

2. Storage and Transport Practices

None of the selected haloalcohols are classified as hazardous materials by DOT. They are shipped in small containers (e.g., 5-gallon glass containers) or in bulk quantities such as in tank cars or trucks (Lichtenwalter and Reisser, 1964).

Since all the selected haloalcohols have low vapor pressures, special storage facilities are not required except that facilities should be constructed of materials which resist corrosion from halogen acid (see above).

3. Accident Procedures

Haloalcohol accidents can be handled by the response procedures standard for organic solvents. The haloalcohols are not especially flammable, and their low vapor pressure minimizes explosion hazard. If spilled, the material can be diluted with water.

Haloalcohol fires can be put out with any extinguishing agent: water; carbon dioxide; dry chemical; or carbon tetrachloride. When burned, the haloalcohols liberate halogen acid (HCl, HBr, or HF). All of these are corrosive and health hazards; the hydrofluoric acid is very hazardous (Sax, 1964).

V. Exposure and Effects Potential

A. Human Exposure and Possible Effects

Potential human exposure to haloalcohols could occur in three ways: occupational contact, losses to the environment from manufacturing plants or industrial waste disposal sites, or use of products containing haloalcohol. Very little quantitative information is available on any of the above sources of exposure.

The haloalcohols manufactured in significant quantities (>1 million lbs annually) are chloroethanol, the chloropropanols, and 2,3-dibromo-1-propanol. With the exception of the dibromopropanol and small amounts of the dichloropropanol which are consumed as solvents, most of these haloalcohols are unisolated reaction intermediates and are both produced and consumed (chlorohydrin process) in the same reactor. Based primarily upon the data of Gruber (1976) and Pervier et al. (1974), it would appear that the chloroalcohols are not among the components of plant emissions to the atmosphere; however, surveys and monitoring studies (see Section II.E.2) have demonstrated that chlorohydrins are released to the environment from effluents and from land disposal of liquid residues (heavy ends from distillation pots). The only quantitative data available on emissions from epichlorohydrin plants comes from Gruber's report which sets the 1,3-dichloro-2-propanol content of water effluents, and residues destined for land disposal at approximately 4 and 2.3 million pounds respectively. Chloroethanol has also been observed in industrial effluent.

Information on environmental release of 2,3-dibromo-1-propanol depict a similar exposure risk from industrial wastes. Monitoring studies

have identified it in water effluent and in landfill leachate. Dibromopropanol has been detected in well water, which has apparently been contaminated with leachate from industrial waste disposal by landfill.

In summary, exposure to haloalcohols from industrial plants is possible. Exposure risk could be high among local populations utilizing water supplies (surface or ground water) near plant effluent release sites or near industrial waste disposal sites.

Few uses of the haloalcohols could result in human exposure. Perhaps the most important exposure risks results from use of foams which are treated with dibromopropanol as a flame retardant. Occupational exposure and perhaps other local exposures (e.g., from wastes or emissions) could result from the use of haloalcohols as solvents, for example, the consumption, of 1,3-dichloro-2-propanol as a plating and metal cleaning solvent.

The inadvertent production of haloethanols and halopropanols could be the most important route of exposure to the general population. These haloalcohols are metabolites produced by reaction of inorganic halide with precursor ethylene oxide or propylene oxide. While both of these epoxides are applied as fumigants to tobacco, grains, spices, and other species, ethylene oxide is also a sanitizing agent for single-service food containers, medical devices, pharmaceuticals and cosmetics. Relatively small percentages of the total annual production of the two epoxides are consumed for these uses; approximately 100,000 pounds of ethylene oxide are annually applied as a fumigant and somewhat less propylene oxide is applied for this purpose. Significant factors contributing to the risk are that the products containing these residues affect the population at large rather than a group limited by

geographical or occupational boundaries and that the affected products include ingested commodities and items that come into close contact with the body. Available information is not sufficient to delineate the average residue concentration contained in these products. Various monitoring studies have noted high concentrations in occasional samples. For example Wesley and co-workers (1965) reported up to 1000 ppm of chloroethanol in whole spices and ground spices, and Gammon and Kereluht (1973) observed ethylene chlorohydrin (chloroethanol) in concentrations of 260 ppm and 310 ppm in flour and spray-dried albumen, respectively. Ragelis (1968) also detected 47 ppm 1-chloro-2-propanol in some foods. Brown (1970) noted chloroethanol concentrations in various surgical equipment, the highest residue found was 27 ppm in heart catheters (woven dacron). Ethylene chlorohydrin residues in medical devices have caused some observed health effects (see below). The regulations of epoxide applications and tolerances on halohydrin residues in the above products (see Section IV.A) should limit exposure. However, it is possible that some products will exceed the limits.

B. Health Effects

The flame retardants Tris and Fyrol FR-2 release 2,3-dibromopropanol and 1,3-dichloro-2-propanol, respectively, after metabolism. Blum et al. (1978) have found up to 29 ng/ml of 2,3-dibromo-propanol in the urine of children wearing Tris-treated sleepwear. Both of these compounds have been shown to be mutagenic in the Salmonella typhimurium system (Blum and Ames, 1977; Gold et al., 1978) and caution has been advised in human use of materials treated with these flame retardants, particularly where dermal and oral contact could result.

Sterilization of food stuffs with ethylene oxide and propylene oxide produces residue levels of 2-chloroethanol and 1-chloro-2-propanol/2-chloro-1-propanol. An estimate carried out by the EPA (1978) indicates that exposure to ethylene oxide residues in foodstuffs by ingestion (0.0003 mg/kg/day) would not result in cumulative toxic effects to man. This is based on a no-effect-level calculated from reproductive effects (Hollingsworth et al., 1956) in guinea pigs. Chronic feeding studies with chloroethanol in rats (Ambrose, 1950) indicate a no-effect-level by this route well above the level expected from human ingestion. The fact that these residues have been shown to produce mutations in the Ames assay (see mutagenicity section) warrants further investigation of long term effects of these agents in humans, particularly cytogenetic studies of bone marrow and peripheral blood.

Adverse effects have been reported after use of ethylene oxide sterilized cardiac catheters or intravenous tubes, due apparently to the formation of chloroethanol residues. These effects include hemolysis (Balazs, 1976), cardiovascular collapse (Lebrec et al., 1978), and anaphylaxis (Poothullil et al., 1975). An estimate for a safe level of residual ethylene oxide in sterilized medical equipment by Balazs (1976) indicates that release of ethylene oxide from polymeric material could produce a genetic risk which is comparable to 10 times the maximum permissible weekly dose of radiation (1 rad gonadal dose). More information concerning the rate of release of the chlorohydrins from various polymeric materials is needed to assess the actual risk factor. The same type of cytogenetic studies needed for evaluation of residue effects from foodstuffs would apply for exposure to sterilized medical equipment, particularly in long term use situations such as are found with hemodialysis tubing and cardiac pacemakers.

Agricultural uses of 2-chloroethanol present exposure risks to workers during application of the compound, both by vapor inhalation and rapid cutaneous absorption. Information is not available concerning the present extent of this type of agricultural usage. However, the reported toxicity of 2-chloroethanol to potato workers (Bush et al., 1949) indicates that inhalation of high air concentrations (300-500 ppm) is extremely hazardous. Animal studies showing the extremely high acute toxicity of inhaled chloroethanol (see Table 13) support this hazard liability.

The haloalcohols have been used as degreasing agents in the cleaning of metal surfaces. Worker exposure by vapor inhalation and direct dermal contact could lead to toxic effects, particularly to the liver and kidneys. Graovac-Leposavic et al. (1964) have reported altered liver function tests in workers exposed to 100 ppm of trichloroethylene (trichloroethanol is a major human metabolite following inhalation of trichloroethylene). Human exposure to chloroethanol vapor at an estimated level of 18 ppm (Goldblatt and Chiesman, 1944) has produced renal effects. Liver and kidney function screening would be indicated in industrial situations where worker exposure was present.

VI. Technical Summary

The ten haloalcohols which have been evaluated in this report can be classified into three groups based upon production volume and uses: 2-chloroethanol and the chloropropanols (2-chloro-1-propanol, 1-chloro-2-propanol, 1,3-dichloro-2-propanol, 2,3-dichloro-1-propanol, and 3-chloro-1,2-propanediol); 2,3-dibromo-1-propanol; and the remaining haloalcohols (2,2,2-trifluoroethanol, 2,2,2-trichloroethanol, and 2-bromopropanol).

While the chloroalcohols are the largest group in terms of production, they are primarily consumed as nonisolated intermediates. Annual production and major use of the chloropropanols are estimated as follows: monochloropropanols (1-chloro-2-propanol and 2-chloro-1-propanol) for propylene oxide production - 1950 million pounds; dichloropropanols (1,3-dichloro-2-propanol and 2,3-dichloro-1-propanol) for epichlorohydrin production - 585 million pounds; and 3-chloro-1,2-propanediol for glycerol production - 195 million pounds. Relatively small amounts (<1 million lbs) of each chloropropanol are consumed for other purposes, such as solvents or intermediates in other syntheses. Chloroethanol consumption is considerably smaller than the consumption of chloropropanols, since it is only occasionally used as an intermediate for ethylene oxide production. Chloroethanol production was estimated at 50 to 100 million pounds per year; an estimate which depends in part upon the amount used in ethylene oxide synthesis. It is also consumed as an intermediate in a variety of syntheses (see Sections II.A. and II.B.).

Dibromopropanol production is placed at <10 million pounds annually. While it was formerly consumed primarily in production of the fire-retardant Tris, tris(2,3-dibromopropyl)phosphate, this use decreased dramatically after Tris was identified as a potential carcinogen. However, dibromopropanol itself is

still extensively used as a fire retardant, mostly in polyurethane foams. Lesser amounts are used as synthetic intermediates (see Section II.B).

Three of the haloalcohols: 2,2,2-trifluoroethanol, 2,2,2-trichloroethanol, and 2-bromoethanol, are produced as specialty or laboratory chemicals. Production of each was estimated at less than 0.1 million pounds annually (see Sections II.A and II.B).

Although the chloropropanols and chloroethanol are produced in massive quantities, their environmental release during manufacture appears relatively small (Gruber, 1976; Pervier et al., 1974). No information was available on the emissions during production (fugitive emissions, vent gases, etc.). Although emissions associated with production appear minor, even a small percentage of the total produced could potentially release several thousand pounds per year (see Section II.C). Wastes generated during manufacture could contain haloalcohols. Studies of manufacturing plants have found haloalcohols in process waters and in heavy ends from distillation pots. Monitoring studies have identified haloalcohols in chemical plant effluents and dibromopropanol in landfill leachate (Shackelford and Keith, 1976; Alford, 1975).

Inadvertent formation of chloroethanol, bromoethanol, and chloropropanol results when the corresponding epoxides react with inorganic halides. The precursor epoxides are fumigants and sterilants for a variety of food commodities, drugs, medical devices, food service items, and cosmetics; estimated application is less than 0.1 million pounds annually for ethylene oxide and somewhat less for propylene oxide. Haloalcohol residues as high as 1000 ppm have been detected in commercial commodities that have been treated with the epoxides, although residues are generally less than 25 ppm (Wesley et al., 1965; Scudamore and Heuser, 1971) (see Section II.C). Haloalcohols that are produced during sterilization and fumigation come into direct contact with humans.

The haloalcohols, with the possible exception of trifluoroethanol, are not persistent in the environment and their chemodynamic properties suggest that they can be transported with water. In water the chloro- and bromo-alcohols hydrolyze. Above pH 9 they initially yield epoxides, which subsequently react to form glycols (Frost and Pearson, 1951). In neutral solutions haloalcohols appear to hydrolyze directly to glycols. In soil the bromo- and chloroalcohols appear to degrade in pathways similar to degradation in water. Enzyme extracts of soil microorganisms catalyze reversible formation of epoxide (Castro and Bartnicki, 1968). The haloalcohols are very water soluble (from 10% solubility to completely miscible) and, therefore, are likely to remain in water until they degrade (see Section II.D).

The haloalcohols have demonstrated fatal toxicity in man following acute oral, dermal, or inhalation exposure. Fluoroethanol is the most toxic of these agents by virtue of its unique metabolism to fluorocitrate and subsequent blockade of Krebs cycle energy production; an oral dose of 2 mg/kg will produce death in rats. Trichloroethanol is the least toxic of the haloalcohols, producing lethal effects at concentrations 30 to 300 times higher than fluoroethanol. Toxicity produced by the other haloalcohols involves gross effects on the central nervous system, liver, kidneys, and lungs. Absorption through the skin is rapid, and dermal contact does not produce marked immediate irritation. Inhalation may result in cumulative effects, particularly in the liver and kidneys. Tissues show depletion of glutathione and other -SH compounds as a result of interaction with haloalcohol metabolites. Fatal toxicity is often seen after a delay of several hours or days following exposure. Autopsy findings of edema in the lungs and the central nervous system indicate that membrane function may be damaged by these lipophilic agents. The haloalcohols are irritating to the eyes, and

direct contact with high concentrations may produce irreversible corneal changes. Some individuals are more markedly sensitive to exposure, developing symptoms of nausea, headache, vomiting, and vertigo at levels that do not produce symptoms in others. This may be due to genetically determined metabolic differences or to damage to normal liver and kidney function. Liver damage produced by the haloalcohols in turn potentiates the toxic effects of drugs and chemicals that would normally be metabolized at this site.

Reproductive effects have been seen with 2,2,2-trifluoroethanol and 3-chloro-1,2-propanediol. The latter has been studied extensively as a post-testicular antifertility agent (see Jones, 1978). Both low-dose reversible effects on sperm motility and oxygen consumption, and high-dose irreversible effects on blockage of the caput epididymis, have been reported following daily administration to animals for 7 to 14 days at 5 to 35 mg/kg. The resolution of the d,l isomers of 3-chloro-1,2-propanediol led to the discovery that the active form in producing antifertility effects is less toxic to experimental animals than the mixture (Jones et al., 1977), which produced bone marrow depression in monkeys (Kirton et al., 1970).

A subacute inhalation study of rats exposed to 0.3 to 3 ppm of 2-chloroethanol has indicated bone marrow abnormalities (Isakova et al., 1971). This included increased numbers of aneuploid cells and chromatid aberrations. However, the pattern of these changes appeared to be reversible with time, thus making it difficult to interpret the biological relevance of these changes.

Investigation of the mutagenic activity of haloalcohols and their metabolites has indicated that several compounds are positive mutagens. 2-Chloropropanol and 2-chloroethanol increased the number of revertants in the Ames

Salmonella bioassay system, particularly in the presence of a microsome-containing liver preparation (Rosenkranz and Wlodkowski, 1974; Bartsch et al., 1975; McCann et al., 1975; Rannug, 1976; Rosenkranz et al., 1975). 2-Chloroethanol has also produced forward mutations in Klebsiella pneumoniae (Voogd and Vet, 1969). Chinese hamster cell mutants have been increased when chloroacetaldehyde, a possible chloroethanol metabolite, was added to the cultured cells (Huberman et al., 1975). Loprieno et al. (1977) have shown chloroacetaldehyde to produce forward mutations and gene conversions in yeast. Both 1,3-dichloro-2-propanol and 2,3-dibromo-1-propanol have been shown to be mutagenic in the Ames Salmonella bioassay system when a liver microsome-containing preparation was added (Gold et al., 1978; Blum and Ames, 1977; Prival et al., 1977). Glycidol, a potential metabolite of 3-chloro-1,2-propanediol, was found to be mutagenic in Drosophila, Hordeum, and Neurospora systems (Loveless, 1966). Trifluoroethanol, however, did not show mutagenic activity, with or without metabolic activation, in the Ames system (Waskell, 1978).

2-Chloroethanol was shown by Verrett (1974) to produce teratogenic effects in chick embryos after injection into the air sac. However, a mammalian study with CD-1 mice (Courtney and Andrews, 1977) in which 2-chloroethanol was fed during the gestation period, did not show teratogenicity.

Chronic studies with 2-chloroethanol given by injection to rats (Mason et al., 1971) have demonstrated an increase in pituitary adenomas, all in the female half of the experimental animals. Balazs (1976) has repeated this dose and schedule of 2-chloroethanol in rats and did not find an increased tumor incidence. Skin painting studies for evaluating carcinogenesis are currently underway with this compound at the National Cancer Institute.

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Conclusions and Recommendations

The following conclusions and recommendations are based upon assessment of available information on the subject haloalcohols.

1. Three of the 10 selected haloalcohols (2-bromoethanol, 2,2,2-trifluoroethanol and 2,2,2-trichloroethanol) are produced in quantities less than 0.1 million pounds annually. Because production is so low, they are considered insignificant.
2. Annual production and major uses of the seven important haloalcohols are as follows:
 - a) 2-chloroethanol - 50 to 100 million pounds annually. The higher end of the production range occurs when it is prepared as a nonisolated intermediate in ethylene oxide synthesis. Chloroethanol is a synthesis intermediate and has some use as a solvent.
 - b) Monochloropropanols (1-chloro-2-propanol and 2-chloro-1-propanol) - 1950 million pounds. They are primarily consumed as nonisolated intermediates in propylene oxide synthesis.
 - c) Dichloropropanols (1,3-dichloro-2-propanol and 2,3-dichloro-1-propanol) - 585 million pounds. They are primarily consumed as nonisolated intermediates in epichlorohydrin synthesis.
 - d) 3-Chloro-1,2-propanediol - 195 million pounds. It is mainly consumed as a nonisolated intermediate during glycerin synthesis.
 - e) 2,3-Dibromo-1-propanol - <10 million pounds. It is mainly consumed as a fire retardant.
3. The release of manufactured haloalcohols to the environment is partially described but incomplete information is available to conclusively describe release factors. Some haloalcohols are released with wastes (presumably destined for disposal by land-fill) and with waste waters. Insufficient information is available on how these wastes are handled.
4. Monochloro- and monobromoalcohols result when epoxides (ethylene oxide or propylene oxide) react with inorganic chloride or bromide. Since these epoxides are applied as fumigants or sterilants for a variety of consumer products, this conversion may expose the consumer population to haloalcohols. The scope of the problem has been partially examined and legal limits on residues have been set by FDA. However, considerably more sampling under actual field conditions probably is necessary in order to examine the extent of the problem.

5. The chloro- and bromoalcohols are subject to environmental degradation. Hydrolysis converts them to the corresponding glycols. Although the nature of the chemical hydrolysis is fairly well delineated, the microbial degradation is not well characterized and it should be further studied.
6. Because of the water solubility of most haloalcohols, considerable method development will be necessary for analysis of these compounds at ppb levels in water samples.
7. Based upon limited bioassay data, the haloalcohols may be regarded as potential carcinogenic agents. Further investigations are needed to establish whether community and/or worker populations are being exposed to these compounds, and if so, what effect has resulted.
8. If it is determined that humans are being exposed to significant quantities of haloalcohols, further mammalian studies will be needed in the areas of: (a) pharmacokinetics and metabolism, (b) confirmation of carcinogenicity and toxicity, (c) in vitro carcinogenicity/mutagenicity, (d) extent and significance of cumulative liver and kidney toxicity. The effects of the haloalcohols on fish, invertebrates, wildlife, plants, and microorganisms should also be evaluated in experimental studies if it is shown that significant environmental contamination is occurring.